PSJ14 Janssen Opp Exh 7 – JAN-MS-02105453

KEY OPINION LEADER

ADVISORY BOARD

defining

RELATIVE ABUSE LIABILITY

for modified release opioid analgesics (MROs) for chronic pain treatment

held in Philadelphia, PA

3-4 November 2003

SACOOR MEDICAL GROUP

International Pharmaceutical Industry Consultants

Chairman: Dr MHA Sacoor MB ChB MRCP

Project Directors: Dr PR Byrne MA MB BS

- **Medical Marketing Research world-wide** - Ad Hoc and Multiclient (with PCPs, Specialists and Opinion Leaders)
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TABLE OF CONTENTS

A. AD BOARD - OBJECTIVES – FORMAT/CONTENT AND PROCESS

A.1. AD BOARD OBJECTIVES

The main goals of this Advisory Board were:-

- firstly, to discuss and develop a package of clinical and other research studies/trials designed to:-
- inform us about the relative ABUSE LIABILITY POTENTIAL of the next generation of MRO analgesics for the treatment of chronic pain
- be persuasive to Clinicians and Regulators of the LOWER ABUSE POTENTIAL of the new generation of MRO analgesics for chronic pain
- secondly, to select from the above-mentioned package the 4-5 KEY 'must have' studies, which to flesh out in more detail, with more specific study parameters, relating to:
  - Study design (hypotheses, rationale, sample, etc)
  - Timelines
  - Costs

A.2. AD BOARD PROCESS – THE NEED TO ENSURE A LOGICAL AND FOCUSED APPROACH WITH THE 'RIGHT' KOLS

A.2.a) Key Success Factors

Our ambitious, over-riding goal - to achieve the most considered, expert and independent advice about the most appropriate study package - could only be met by fulfilling the 2 following pre-requisites:-

- firstly, by selecting our KOL/Expert panel objectively, i.e. on the basis of peer-group acknowledgement and nomination, and ensuring that we covered the relevant sub-disciplines, such as:-
  - epidemiology/surveillance
  - pain and pain addiction
  - abuse liability testing
  - diagnostic categorization
  - ethnographic studies / Qualitative studies
  - physical chemistry/formulation
  - street chemistry/Clandestine laboratories
  - DEA perspectives
- secondly, by ensuring that all the invited KOLs/Experts had had the opportunity to reflect on – in the run-up to the Ad Board – what they perceived to be:-
  - the research studies which would (in their view) be most persuasive to Clinicians and Regulators, in demonstrating the lower abuse potential of the next generation of MRO analgesics for chronic pain

The approach taken in respect of these two major success factors is described below.

A.2.b) Identification and Selection of the KOLs - our unique OPEX™ methodology

Our OPEX™ methodology is the most systematic, comprehensive and objective way of economically **identifying and profiling** Top Peer-Group Nominated Opinion Leaders in any subject area, and in any country or group of countries.

OPEX™ is not only about identifying the top peer group nominated Opinion Leaders but also about detailing their interests and experience objectively, so that you are able to select the most value added individuals.

The OPEX™ process and its 'unique' key benefits

The OPEX™ process is specifically designed to:-

- eliminate the bias and subjectivity associated with the traditional and other identification methods
- highlight the Opinion Leaders who are the most value-added individuals from the Pharmaceutical Company's point of view, and to
- provide genuine objectivity in management decision-making (whether selecting candidates for a strategic advisory board or speaking engagement, or putting together a cutting-edge clinical trial group); the bias mentioned above is basically inherent in methods which rely on subjective judgements and limited systematic assessment of the Opinion Leaders' academic background and experience

OPEX™ achieves its goal by employing a series of powerful techniques, involving:-

- technologically advanced software
- electronic database searching
- extensive traditional market research
- ongoing data entry and digital analysis, and
- constant hands-on input and monitoring

OPEX™ projects are conducted by a team of highly qualified and experienced executives dedicated to managing the OPEX™ process within our organisation.

OPEX™ is essentially a two-step process, involving:-

- firstly, an electronic database search (using Medline, Embase, and other key international literature databases) to identify the Top Authors publishing in the target topic around the world
- secondly, contacting those Top Authors by mail, fax and phone to ask them who they themselves regard as the top Opinion Leaders in their own field

This approach has the key benefit that by identifying and then asking the people most actively publishing and working in the target topic to make their own assessment of Opinion Leadership, we are able to identify truly objectively, systematically and comprehensively, the Top Peer-Group Nominated Opinion Leaders.

The OPEX™ approach was used to identify the most appropriate KOLs to be invited to the Ad Board. The list of potential KOL candidates was then modulated in accordance to other factors related to Janssen.

The names and affiliates of the 14 KOLs who attended the AdBoard are shown overleaf.

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A.2.c) Pre-Ad Board Task

In order to fulfil the second pre-requisite, we asked each invited KOL/Expert to:-

i) **Think** about the 5 or 6 (or more if appropriate) types of studies/trials that might be appropriate to include in the total package, which would be most persuasive to Clinicians and Regulators of the lower abuse potential of the next generation of MRO analgesics for chronic pain.

The KOLs were invited to include any type of study e.g. Epidemiological, Clinical, Ethnographic, related to Physical Chemistry, Pharmaceutics, Formulation or Street Chemistry, or indeed any other category not specified here.

ii) **List and briefly summarize** for each study/trial the following key aspects (including but not exclusively):-

- rationale for study (hypotheses to be tested)
- study design (sample size, outcomes)
- interpretation
- potential risks
- other relevant aspects

A.3. AD BOARD FORMAT/CONTENT

A.3.a) Summary of Overall Ad Board Flow

The Ad Board was conducted over a 2 day period (3-4 November 2003) in Philadelphia, and consisted of the following FOUR parts:-

PART I Monday 3 November – (8.15 am to 1.00 p.m.)

- The first part consisted of a number of 'profitable' 'Ice-Breakers' in the form of a series of 10-minute **informal presentations** on pre-defined topics (in the context of our main goals).
- The intention was for each of the KOLs/Experts to speak in an **informal** way about their allocated topic, and to give their opinion in the context of our main goals.
- Opportunities for clarification discussions were interspersed between the Ice-Breaker presentations.

PART II Monday 3 November – (2.00 pm to 4.00 pm)

- Summarization and categorization of the Thematic Study Outlines suggested during the pre-Ad Board survey.
- Discussion of key aspects of each trial/study Thematic Outlines.
- Prioritization of studies to determine the 4-5 KEY 'must have' studies/trials .

PART III Monday 3 November – (4.20 pm to 6.20 pm)
Tuesday 4 November – (8.00am to 10.00am)

- Break-out sessions in which participants convened in small groups, each one working on a particular type/types of study and assisted by a Medical

Writer, to map/flesh out Clinical trial/study protocols specifying the relevant details of:-

- trial design
- time lines
- costs

PART IV Tuesday 4 November – (10.30 am to 1.00 pm)

- Presentation to the entire Ad-Board of the protocols of each of the finally selected clinical trials/studies, and discussion regarding:-

- further development/refinement
- modulation
- fine tuning

The Advisory Board ended with Lunch at 1.00 pm on Tuesday 4 November.

A.4. DISCUSSION – CATEGORIZATION AND PRIORITIZATION OF SUGGESTED STUDIES

A.4.a) Process of Categorization of Suggested Studies

In terms of the process of more detailed discussion, categorization and prioritization of each Thematic study outline, the following process was adopted in open discussion with all members of the Ad Board, i.e. the KOLs were asked to:-

- firstly, define whether the study should be considered as part of the total study package which would be persuasive to Clinicians and Regulators of the lower abuse potential of any MRO
- then, to specify whether:-
  - the study could be started pre-launch or had to be started post-launch
  - the study could be done within one year or required longer to complete

Then for those studies that were defined as potential components of the package as described above, the KOLs were asked to assign their level of priority (as part of the package) by giving their opinions along two dimensions:-

- firstly, to give their overall opinion by specifying whether the study was regarded as a 'must have' or a 'nice to have' within the package
- secondly, to give their more individualized opinion by rating the level of importance of that particular Thematic study outline (as part of the package) on a 1 – 5 point scale, where:-

- *1 = not critical as part of the package, and*
- *5 = absolutely critical to the package*

Finally, the KOLs were asked to consider that – if the challenge was to construct a clear and credible, persuasive package, utilizing only those studies that could be conducted within one year, how would they go about selecting and possibly modifying some of the studies already discussed. The goal here would be to construct a persuasive argument for lower abuse liability, (compared to other opioids) just with those studies of 1 year or less duration.

The KOLs were then sub-divided into several break-out groups, each one assisted by a Medical Writer, and charged with developing outline trial/study protocols for the specific trials which had been defined as 'must have' components of the trial package as described earlier on in this Report.

These outline protocols were prepared using a common template that had been provided to all the break-out groups beforehand.

After the protocols had been designed, the Advisory Board re-convened (on the following day) and the protocols were presented to the entire Group for further discussion and elaboration. This approach was designed to ensure that all the KOLs would have an opportunity to comment on the output of all the break-out groups, not only their own.

A.4.b) Results of Process of Categorization and Prioritization of Suggested Studies

The pre-Ad Board Task was highly productive, resulting in a total of 59 studies being nominated. These studies were then condensed into 25 Thematic outlines, and further consolidated into 5 major study types/categories The details of the analysis are as follows:-

- Total number of study suggestions = 59
- Consolidated into Thematic study outlines = 25
- Grouped into Study types = 5
- Thematic study outline breakdown into major study types – as follows:-
  - - Qualitative studies = 3
  - - Clinical Trials = 5
  - - Epidemiological studies = 7
  - - Human Experimental studies = 8
  - - Chemistry studies = 2

The idea behind the Thematic outlines was to enable the handling of situations where two or more KOLs had suggested something similar, which, whilst not

identical, did not merit totally separate consideration or discussion. In any case, the names of the original study proposers/sponsors were mentioned alongside the Thematic study outlines, so that each KOL could see clearly exactly where their own suggested studies had been categorized.

The 25 Thematic study outlines were (later on in the process) further consolidated into:-

- 12 potential study/trial protocols, which were further reduced to:-
- 6 Key protocols, which were then outlined in more detail within the KOL breakout groups, and were the end deliverable of the Ad Board

There were 5 Breakout Groups, each one addressing one of the 5 study types. The KOL composition of each break-out group was primarily based – as far as possible – on who had proposed which study. This approach was designed to maximize the level of efficiency of discussion within each Breakout Group, by ensuring that the KOLs designing the relevant protocols were the very same ones who had suggested those particular studies (or types of studies).

In the event, the Breakout Group composition was as follows:-

- Qualitative studies = Budman, Henningfield and Siegal
- Clinical Trials = Passik, Portenoy and Rounsaville
- Epidemiological studies = Chilcoat and Vaughan 7
- Human Experimental studies = Jasinski, Kosten and Zacny
- Chemistry studies = Bianchi and Coleman

B. DETAILED POINTS/ISSUES DISCUSSED DURING ICE BREAKER PRESENTATIONS

B.1. CHRONIC PAIN – AN ENORMOUS PUBLIC HEALTH PROBLEM (BASED ON RUSS PORTENOY'S PRESENTATION)

B.1.a) Chronic pain is an enormous public health problem.

And we now have an enlarging data set to establish that reality.

3 recent studies/publications to support this:-

- new study done in Europe of over 26,000 individuals, a community based study, showing that chronic pain is suffered by about 25%.
- recently completed a trial (by Russ Portenoy)
  - a population based telephone survey of Caucasian Hispanics and African Americans in the United States
  - about 1600 individuals
  - showing that **persistent and frequent pain afflict about 30%**
- Portenoy recently had a paper published about 4-5 months ago in JAMA –
  - looking at the prevalence of chronic pain
  - in patients who are being treated in methadone maintenance programmes or
  - in residential drug treatment programmes and it
  - shows that **chronic pain is a significant problem in about 40%**.

So if you look at the surveys that have come out during the past 15 years or so

- incidences tend to vary somewhere between 5 and 40%
- modal number is around 15-20% with some being higher.

So when you are talking about the total population, you are talking about millions and millions of individuals who have frequent or persistent chronic pain, enough to produce some element of disability.

Then the question is:-

What proportion of those patients should be treated with opioid? Probably a very small proportion, and yet it's been clear that under-treatment was the typical response.

(1) Historically – 3 phases of treatment

(1) Phase One - Before the 80's

Innumerable surveys show that:-

- even in populations where there was a general feeling that opioids should be used, like **the cancer population with advanced illness**, opioid use was uncommon, and under-treatment was a huge problem..

Phase Two - The early 80's and through the early 90's

- there was an **intensive effort to educate oncologists**, much of it by pharmaceutical companies like Janssen, which resulted in an international understanding that:-
  - **opioids are preferred** in the management of moderate to severe pain associated with
    - cancer
    - AIDS and
    - other advanced medical illnesses

At the same time there was:-

- a very gradual movement to think about the **use of opioids for chronic non-malignant pain**.

There was a:-

- **large literature that suggested that it should never be done, then**
- **slowly expanding literature suggesting that some patients are going to benefit.**

All this culminated in an **important watershed event**:

- the publication of a **consensus document** jointly by the American Pain Society and the American Academy of Pain Medicine that essentially said:-
  - that there is in fact a **sub-population of patients with chronic pain**, who **should be treated with opioids** because
    - they act like the usual cancer patient. They gain sustained benefits without the loss of efficacy due to tolerance or any other factor. Their side effects are tolerable in a way that would be safe and effective

Abuse and addiction as a potential – mentioned and were already inhibiting them from going forward - so **they had to get past it** - and the

Oxycodone problem has led to a **wake-up call**

Now the **goal is balanced** and the perspective on the issue of balance is that it's both at a

- national level and
- an individual level.

At a **national level** the goal is to:-

- continue to identify those patients who would be appropriate candidates for long-acting opioid therapy and at the same time
- recognise the need to have controls so that abuse and diversion are minimised.

At an **individual level** what this means is that:-

- every patient who is being considered a candidate for these drugs has to:-
  - undergo a **risk-assessment by the clinician** and
  - an appropriate element of the prescribing has to be risk management
  -

Phase Three – Mid 90's to date

So that brings us to the next level (3) which is what's going to happen now at the level of the individual prescriber:-

- the use of opioid drugs is going to continue to grow in primary care and
- that's going to be
  - contingent of course on a facilitatory environment on the part of government and law enforcement
  - driven by studies, most of which are going to be funded by Industry. What the studies will show hopefully is that there's
    - an element of safety and also
    - a manageable level of risk of abuse that can be dealt with so that
    - clinicians feel comfortable in selecting patients for this therapy and then using it over time.

B.1.b) Future trends

So the question is, if that's going to happen….
what's the likely trend with respect to some of these newer formulations that are going to occur???. Because **modified release opioids are a rage** and every time you turn around there's a new one on the market.

Physicians are very happy about this choice – they like having a lot of products in the marketplace - particularly given **the extraordinary intra-individual variation of response to different drugs.**

But with respect to the **modified release opioids**, the high likelihood is that :-

- as the concept of opioid prescribing for chronic pain continues to get out into primary care and
- as primary care physicians begin to feel more empowered by having an understanding of
  - the principles of prescribing, and hopefully at the same time
  - an understanding of risk assessment and
  - risk management
- the drugs they will turn to are going to be these **modified release opioids**

WHY???

Because:-

- that's where the studies are showing safety and efficacy
- that's where the advertising is.

So the use of these drugs will continue to grow, not only:-

- because primary care doctors will begin to use them but also
- because the problem of chronic pain is so enormous that
- the proportion of patients who are candidates for opioids who aren't receiving the drug is likely to be very large.

B.1.c) Comments about Risk Assessment

There are three key players in this scenario:-

- Addiction Specialists – concerned mainly about:-
  - **addiction** and
  - **abuse**
  - defining it and
  - measuring it
  - in populations **who have not been given** a drug for legitimate purposes
- Law Enforcers and Regulatory people – concerned mostly about:-
  - **diversion**
  - in populations **who have not been given** a drug for legitimate purposes
- Pain Specialists - are worried mostly about
  - Diversion
  - abuse and then
  - misuse
  - in populations **who have been given** a drug for legitimate purposes

it's very important to recognise that from the perspective of pain specialists it's not just about abuse and addiction,

The Challenge of doing Research in this area ….

The challenge is:-

- in figuring out how much liking is enough - not too much
- in understanding all of the elements involved and their interaction in the Risk Assessment bucket.
  - **As they apply to the population of patients with chronic pain i.e.**
- to **go beyond a highly sophisticated and evolved methodology** for looking at abuse issues in populations with no target symptoms. And to think through:-
  - how does one now evaluate populations with target symptoms? and
- to try to sort out the distinctions between
  - Misuse
  - abuse
  - addiction and ultimately
  - diversion as well

B.2. PAIN PATIENTS ??? A SPECIAL CATEGORY OF PATIENTS ???? (BASED ON STEVE PASSIK'S ICE-BREAKER)

B.2.a) Minimally monitored drug only pain therapy

Not just that these patients are **going to be treated by primary care** but they are going to be treated with an insurance industry that mandates a new catch phrase which is:-

minimally monitored drug only pain therapy, and if the insurance industry continues to force people into minimally monitored drug only pain therapy they are going to get **a lot of opioids with little monitoring** and that will work fine for little old biddies with arthritis but **it won't work well for people with higher vulnerability and addiction** who get exposed in the pain setting.

B.2.b) What happens when you do research amongst non-compliant (not addicts per se) people who get exposed to drugs for pain???

Basic premises that prompted research specifically with this group of patients**:-**

- the idea that we needed to have a little bit more knowledge about the:-
  - epidemiology and
  - frequency and
  - meaning of problematic behaviour in pain patients.

- we in the pain clinic
  - have our own phenomenology that
  - the phenomenology of addiction often doesn't fit when we go room to room talking to
    - cancer patients
    - chronic pain patients

B.2.c) Behaviours in the pain setting

We will see people who are more or less taking their medicines as prescribed and the **behaviours that come up in the pain setting** will have a pretty big spectrum:-

- some of them are fairly common and not very worrisome on their face value
- some of the are uncommon but illegal and we will see all of this

And we've been trying to teach the pain community to:-

- dialogue with patients and
- get a flavour for how often these things happen and then
- understand their meaning.

There are multiple aetiologies of those behaviours, that's the problem we have in the pain management setting. We see a lot of:-

- non-compliance, potentially aberrant behaviour

But - how do we sort out:-

- which ones are related to **addiction and abuse**
- which ones are related to **inadequate analgesia**,
- how often do we see **chemical coping** where people are using their medicine in less than fully compliant ways, as a result of a range of situational stresses or psychiatric comorbidities, that they are self medicating
- how often are these behaviours
  - running out and needing early prescriptions as a result of **diversion and criminal intent**

We don't know how often they link up to these various aetiologies.

There are a lot of different types of bad outcomes, that we can see in the pain management setting e.g.:-

- some abuse or misuse
- we'll see out and out addiction but it's probably low in those who are not vulnerable and then we will see
- a whole range of **middle ground** where we see aberrant use patterns but not necessarily compulsive or out of control. They are always though
  - on the fringes of what we consider appropriate drug taking and generally
  - pain clinics tend to be full of these kinds of patients who have these kind of patterns

So we see a whole spectrum. We don't even know how common any of these various ones are.

Steve has a NIDA funded study looking at these kind of outcomes.

B.2.d) Behaviours in the setting of AIDS and cancer

So what does the field look like – based on studies of aberrant drug behaviour l in:-

- AIDS patients(addicts with pain, who were on opioids)and
- cancer patients?

- AIDS patients average 6 of those aberrant behaviours per patients in a 6 month period
- cancer patients just under one and a half

Breakdown is towards the ones that were on the less severe side of the slide more commonly. When you look at these, and this is what you saw earlier but in graphic form, I wanted to point out .

Something very interesting –

- cancer patients are shifted towards lack of aberrant behaviours

- addicts with AIDS who have pain are shifted towards aberrant behaviour 9that's understandable **but**
- **6-10% of cancer patients** population has **some vulnerability to addiction**.
- **Same with chronic pain patients -** same pattern, where a
  - small sub-set somewhere **between 6-10%** are having a lot of aberrant behaviour – i.e. are vulnerable as well
  - like 6-10% of radio talk show hosts are vulnerable to addiction.

B.2.e) Pseudo-addiction

Pseudo addiction is discussed a lot in the pain community

People:-

- acting out of desperation and
- taking matters into their own hands and then
- acting in a fashion that looks like addiction but
- are really **driven by uncontrolled pain**
- but in **study of addicts with AIDS** who had pain
  - with a simple rough formula to calculate adequate vs. inadequate analgesia, that had no bearing on the number of aberrant behaviours and
  - no bearing on the ratio of less severe to more severe.

So in certain populations, pseudo addiction which is not empirically validated would have to be applied cautiously.

Remember also that:-

- the **diagnosis of pseudo-addiction** is made after the fact when the under-medicated patient is properly medicated and if the addictive behaviour is dissipated then that might be considered pseudo-addiction

Steve has developed, (with Janssen's help) :-

- an assessment/documentation tool (chart)
- to give to pain clinicians
- to allow them to d a better job of following the 4 As.

KOLs see pseudo addiction in every day practice

It really is a real important notion.

Steve is currently reviewing a couple of papers for publication where some big pain clinics have gone back and tried to look at aberrant behaviour in their samples, and one of the things they keep finding is that **dose is associated with aberrant behaviour** – which is a bad thing.

Is it to do with BAD TEACHING ???

It suggests that we are teaching this to people that write off a lot more pseudo addiction potentially.

if you really were teaching this right:-

- pain clinicians would reserve higher and unorthodox doses for model drugs takers

But that's not what happens in the real world, either

- because they have nothing else to offer or
- because they don't know how to stop the drugs, or
- because they are writing it off as pseudo addiction.

A good example is sickle cell patients – they are always stigmatised.

All the oncologists were sending them over.

And we got a lot of them on adequate pain therapy and some of them had to be reported to the DEA because they continued to divert and a lot of them settled down.

So the issue is very hard to figure out in the clinical setting, but we see it every day.

And, it is not an empirically validated notion particularly. The original paper from 1989 had only two cancer cases, when Wiseman and Haddocks first wrote the paper.

However ……

Frequency of aberrant behaviour in chronic opioid therapy patients – over a 6 month period

- 45% of the sample has them
- 6-10% of the chronic pain patients had as many behaviours as an addict population did

Pain clinicians are not infrequently confronted with these behaviours. Nobody in this room would think that all of those patients are addicts because of all those other factors that play into the emergence of these behaviours in the chronic pains setting.

B.2.f) Eastern Kentucky experience at the height of the OxyCodone abuse epidemic

- 195 admissions to substance abuse unit for OxyCodone
- OxyCodone abusers on average were using 180 milligrams a day
- all had other DSM4 non-substance related diagnoses
- all had histories of poly-substance abuse, and
- a history of other prescription drug abuse as well
- were younger - male - and rural - as compared to the other users.

But – there was a very controversial but important sub-set:-

- **60 of these patients** were ostensibly begun on the drug during pain management and
- were started primarily by primary care and other non-pain experts.

Again the problem of the **vulnerable group** perhaps when they are treated with **minimally monitored drug only pain therapy**, which is basically the only kind of therapy you could have gotten in Eastern Kentucky.

They had very similar – in fact identical - medical and demographic and psychiatric comorbidites as compared to the other OxyCodone abusers, i.e.:-

- were equally likely to alter the route of administration and
- 13% of those patients were reported crushing and injecting the drug.

So the fact that you get exposed during pain management might not mean that you wouldn't do the really weird stuff if you were a vulnerable patient.

But, interestingly, that they look at lot like the other users insofar as perhaps:-

- pain primary care guys did not take a full psychiatric and substance abuse history on these people.

We might have located them in a more vulnerable sub-group had they done that.

So, basically:-

- these behaviours are not infrequent and therefore
- **a product safety issue is really important**, and **even if you started in the pain setting** - if you are a vulnerable patient, you might try to alter the delivery system or do the kinds of things that people who started recreationally might try to do.

B.2.g) How did the OxyCodone epidemic begin ???

Orthopods starting using OxyCodone a lot as opposed to other medications and sending people home with OxyCodone.

The first patient one of the KOLs saw was somebody that:-

- had had knee surgery in June and
- in September he was up to 800 milligrams a day of OxyCodone

They didn't know particularly what to do with him so part of this was naivety on the part of the orthopaedic surgeons.

So other than primary care, there were are others.

Just that for some reasons **a lot of surgeons took to OxyCodone**

WHY???

- they were advertised to for one thing and then
- there were a couple of post-op pain studies done and the rest is history.

B.3. PUBLICLY AVAILABLE NATIONAL DATA SETS (BASED ON ROGER VAUGHAN'S ICE-BREAKER)

B.3.a) Firstly – regarding abuse potential

Take a three lens look - what sort of data sets should we be looking at ???

If we are going to be looking at **abuse potential**,

- first - the drug has to be **available** - . So we look at the data sets that might tell us be informed of how much of each particular drug is around and available
- second - look at data sets that might be informative about the **incidence and prevalence of abuse**
- third - what are the **consequences**- what happens to people when they misuse and abuse and how do we measure that.

So this is trying to look at the 30,000 foot level, overall what's the situation

Data sources for availability:-

Two main data sources are:-

- **ARCOS**
  - managed by DEA
  - looking at the distribution of legal prescription drugs as they move around the country, and
  - in terms of manufacturing
  - the unit of measurement there is grams
- **MPA** which
  - looks at the number of prescriptions
  - in terms of number of prescriptions.

Limitations of these data sets

ARCOS

has a little bit of a glitch in that they

- changed the collection procedures between '96 and '97 so it's also informative to look at the data in those two time periods

As we already know, in the past 5 years there has been a great increase in distribution of OxyCodone, and methadone and reductions in codeine.

But what does not show up at first glance (because it would just blow away the Y axis) is fentanyl. In the early 90s about 1000% increase in the distribution of fentanyl and it's reduced a bit - but only to about 150% increase over the past 6 years.

Then **if we look at prescriptions**, (compare to the ARCOS data that was looking at the manufacturing and distribution) this is in terms of number of prescriptions, and :-

- we just look at opioids
- we look at hydrocodone –
  - 75 million prescriptions in 2002
  - current estimates are that there's about 3 billion prescriptions written a year
  - the 75 million prescriptions written for hydrocodone make it the number one prescribed drug in the nation, followed by:-
    - Lipitor and may be
    - amoxycillin

Over the past 10 years:-

- overall **500% increase in opioid prescriptions** – in the backdrop in the last 10 years of
- a 12% increase in population in the United States

So it certainly is outpacing our population and prescriptions in general.

The pros and cons

ARCOS is

- the only way that we can **track where these drugs are moving around the nation** and in certain cases it's
- quite informative to pinpoint **where are the hot spots** of where these drugs are moving.

MPA

- helps us look at **how many prescriptions are being written** but - it just says how many are written – its:-
  - not looking at per person
  - not looking at how many people are getting how many prescriptions and
  - certainly not trying to find out is a three week prescription or is it a three month prescription.

So it says in general how much but it may not be informed about abuse.

Is it that we are supplying the appropriate amount of drugs and prescriptions or is it abuse???

The utility of this data set for our purposes may or may not be helpful.

B.3.b) Secondly – regarding abuse

There's really **only one national data set** that can help us look at that – i.e.:-

- the national household survey, now called the NSDUH but used to be called NHSDA which 'rolls off the tongue much better', so people continue to call it NHSDA.

NHSDA is

- a population based household survey
- performed every year since about 1973.

One of the issues - in terms of using this as a data set that can talk about abuse is that:-

- the question that NHSDA uses to be informed about misuse is:-
  - 'have you ever used a drug that was not prescribed for you or was only taken for the feeling that you got'.

Well, is that:-

- misuse
- is that abuse, or
- is that just finishing off the three pills that you had because you hurt your arm?

Although they do have the DSM4 criteria for dependence, that too mixes:-

- physical dependence and
- psychological dependence

Some highlights…..

- **marijuana** prescription drug misuse - is defined at about 5% of the population
- in terms of DSM criteria - dependence is estimated at about .4% - not too distant from other listed drugs which include heroine, cocaine and inhalants.
- of the total number of people on prescriptions drugs we get **about a million people** who are **estimated to be dependent on prescription drugs** - again not too dissimilar from the number of people who are dependent on cocaine and heroine.

But – are these estimates low ??? Probably ….

Among those people who misuse - what's the probability that you become dependent ???:-

- about half of heroine misusers are dependent so you can look at about a 50% chance of becoming dependent and
- opioids just about an 8% chance

Incidence and prevalence rates as calculated by NHSDA

- the incidence and prevalence rates as calculated by NHSDA again vs. heroine and cocaine where the new users tend to go up between 28% and 165%
- opioid new users or experimenters 276% in the last 10 years
- the **troubling thing** is that the **prevalence is also rising** so it's not just experimenters, it's that more people become habitual users

Pros and Cons

- the pro is that its what we have. However, the problem is that
  - there is clear evidence of **under-estimation** - The NHSDA estimates **about a million** hard core drug users, other estimates **say about 4 million** – so there's clearly a miscommunication there.
  - **weak definition of abuse** – what do we actually mean by that, what does that misuse mean or what are we measuring.
  - It's a **three year lag** in information
  - they only **report it as all opioids**. - So in terms of trying to get specific about - is it fentanyl, is it OxyCodone? We are not going to be able to tell using that.

What does the NHSDA tell us about consequences???

Reported consequences:-

- people who use stimulants and sedatives –
  - they report problems that look more like heroine and cocaine or opioids and tranquillisers,

- much less number of people report emotional problems and health problems.
- in the ED mentions, – in the context of about 500,000 mentions - you can see huge numbers of mentions for cocaine and heroine, but
- not that many for opioids.

The problem is though that the number of mentions across the past 10 years is increasing much more rapidly than for cocaine and heroine.

So the idea of using DAWN or the ED mentions as an indicator of abuse again is troubling because most of the mentions are multiple mentions.

You show up at the ED not just for one thing but for multiple things and so they are going poly-users - did you show up because you had an opioid problem, probably not, it was probably multi-drug.

And as outlined as well the typical person who shows up at the ED is probably not, as NHSDA shows, is not the typical prescription drug abuser. So the populations are very different.

B.4. THE CONCEPT OF 'HALO-DEMIOLOGY' (BASED ON HOWARD CHILCOAT'S ICE-BREAKER)

B.4.a) What can Epidemiological Research contribute – towards defining abuse liability

Lots of trade-offs between people doing:-

- basic research and
- clinical research and
- laboratory data research

Lots of ways for all these disciplines to work together to inform each other.

The important aspect of epidemiological research is that it's:-

- population based and
- can define the population in different ways – we use:-
  - national samples but also we can use
  - sub-groups
  - certain communities and then of course here there's going to be a focus on
  - pain patients as a population.

We define that population and that gives us a **denominator** to work with, and then we want to look for the **numerator** – i.e. numbers of cases emerging in that population.

What is a numerator and what is a denominator???

They are two important things that we have to measure as well as possible in order to estimate incidence and prevalence of some outcome e.g.:-

- abuse and
- dependence
- or any other defined outcome

Epidemiological (longitudinal) research is **important and useful** because:-

- it of **minimises a selection bias** - we can draw samples from this defined population
- it is the only way that we can **understand the natural history of disease** in a sense, especially we are
  - talking about dependence and
  - watch it unfold, and
  - we can see that there are going to be different courses for different individuals and we
  - can only understand that by looking in a population i.e.:-
    - defining the population
    - following forward to really understand how these difference courses emerge
  - controlled temporal sequencing which is important – that's the only necessary but not sufficient criterion for demonstrating causality

B.4.b) Understanding the heterogeneity of drug use outcomes

Epidemiological research can help shed light on this in terms of:-

- trajectories that different individuals have
- different rates of onset of use and
- escalation of use

Possibility of re-defining more relevant/appropriate types of outcomes

When we talk about outcomes we typically use:-

- abuse or
- dependence - as a diagnosis

But, and especially for the purpose of what Janssen might be looking for, we might want to look at a range of classes of responses and, for example:-

- there may be certain sub-groups of symptoms that
- can be grouped together
- empirically as well as
- conceptually

There could be 3 sub-groups in the population:-

- primarily a large group of individuals who are prescribed for pain, and who have no problems
- a group of people that may have some kind of moderate distress in terms of the problem and they may have certain sub-groups of symptoms but not full blown dependence. And then probably there will be…
- a small class of individuals who have full blown dependence and have everything. And we can use methods like latent class analysis for example to shed some light on that

Stages of progression

We are interested in stages of progression of use.

If we are talking about typical extra-medical use of drugs, for example:-

- cocaine
- heroine
- analgesics that people use on their own, there is:-
  - opportunities to use which is related to the availability of the drugs in the population
  - a diversion, you can't use the drug unless you have an opportunity then you initiate use
  - progress to dependence and also there's
  - some remission that goes back and forth. Most people quit on their own that have problems, for certain drugs any way, and in certain pain

medication too you have opportunities to use in terms of your prescribed medication so you have a higher opportunity but then when you initiate extra-medical use and then that escalates

There's a lot of trajectories that people can have and we can characterise those if we have the data.

- some people may obviously have no problems
- other people escalate quickly and maintain high levels of use,
- some people may have used and have a steady increase.

B.4.c) Vulnerability

How does one define vulnerability???

Who is vulnerable???

Obviously not everyone is vulnerable to the dependence.

So we have to consider efficient sampling.

So if we are going to do a prospective study, we want to:-

- follow up 100,000 people when
- the majority of them aren't going to develop problems

Are there some ways to identify people who may be at higher risk to follow up???.

And then, of course, in terms of practice, effective prevention and minimisation of risk.

And when we talk about vulnerability, what, is it:-

- dependence, or
- some specific symptoms that we are interested in or
- psychological distress related use,

what are you vulnerable to???

Most people really aren't vulnerable and aren't going to have any kinds of problems. And then **other people** have problems and develop them quickly.

Some people might be vulnerable in a sense, say **genetically** however we define it, don't develop problems and some do and they have different onset at different times.

And so we might just want to **over-sample** or get everyone, if

- we can define in some way a vulnerable population
- we have some kind of **screening approach** or something that is relatively
- sensitive and
- specific

We could **over-sample** or sample all the people that are vulnerable

Example of data from a vulnerability study

National co-morbidity study – another national survey:-

- that was done about 10 years ago now,
- there's a follow up – and
- there's another survey that's coming out that will be useful ;Bridget Grant study,

The national study of **alcoholism in related conditions**, the NESARC study that:-

- will be coming out in January for public release,
- about 50,000 people that have a lot of co-morbid information

The National Co-morbidity Study data for analgesic dependence is limited:-

- we don't know how they got the drug
- we don't know if they were prescribed them and started using more or
- if people use them on their own.

But what you do find is

- the characteristics, the big factor **anti-sociable personality** people are about 15 times more likely to develop problems from these disorders.
- if you have a **previous history** of cocaine dependence you are also a lot likely to develop these problems as well as other psychiatric symptoms - but a lower magnitude.

Is vulnerability consistent across all opioids???

It might vary ….

B.4.d) How can we integrate epidemiology with other research activities?

We can inform laboratory based studies in sampling for abuse liability studies, e.g. in:-

- case control studies where we can
  - sample individuals for a prospective study for
    - specified biologic measures
    - genetic markers
    - other kinds of psychological tests - neuropsychological testing.
    - prospective screening
    - oversampling
    - minimise selection biases
    - look at the heterogeneity of outcomes

B.4.e) How to define the population to follow up in epidem studies???

The model of **opportunity initiation,** seems to be a bit problematic when we are talking about:-

- a population of people,
- sub-identified as patients
- who get a drug for their target symptom –

So the question would be - in terms of population based studies:-

- how do you define an inception cohort that you might want to follow prospectively –
  - if you can't use just the mere administration or the regular use of the drug as an indicator of the population to follow?
- how do you define the sample with more clarity so that we are not trying to follow 100,000 people for 5 years,

This is a **very big issue** and the problem is:-

- if you are taking a vulnerable population,
- if you are not talking about patients
- is **anybody who has used a schedule 2 drug**. E.g. the extra-medical use to be included in your vulnerable population and you follow them.

Answer - you could use some kind of sampling approach based on prescription records - that's our population - people who have at least one prescription…..

There are ways to define our population that way.

You wouldn't want to have a broad net, but then you **still need to follow a lot of people** to get a lot of action.

So may be then you could use screens for example. - to screen a large number of people, - **if we had a good screening instrument for vulnerability.**

B.4.f) An ethical issue/dilemma –

In defining screening criteria and following up a selected cohort in an epidem study

Suppose for example you wanted to use an aberrant drug related behaviour to define your cohort – because you can't use just use using the drug - so you have to use the fact that they've done something bad……

The problem is - if they've done something bad then ethically the doctor's got to try and correct that. And then **you can't do epidemiology any more**.

So the question would be -

- do you want that screening to be **the drug using behaviour** or
- are there **other factors** that may be we would want to screen on that
  - aren't related necessarily to the drug user behaviour but
  - are in terms of other psychopathology, such as for example:-
    - other earlier behaviour problems
    - history behaviour problems
    - certainly demographic characteristics
    - age groups (some are going to be higher risk than others)

You would definitely want to use other kinds of markers and not use the drug use - as the optimum – because:-

- .if you start when they've already got aberrant behaviours then you are capturing when the process has started and you really want to ideally:-
  - get it as an incidence study as they emerge – but we don't know how practical that is

B.4.g) The Vulnerable Community

THE VULNERABLE COMMUNITY – i.e. one should focus NOT just on the vulnerable individual but on the VULNERABLE COMMUNITY

Because what you are interested in is **diversion and diffusion** into vulnerable populations.

So it suggests that your epidemiological research might:-

- focus on a vulnerable community rather than individuals who have been prescribed the drug, and
- we've got methods to actually study this prospectively and
- that's where the OxyCodone issue caught a lot of people 'with their pants down' - We had no idea that it could move out from the people who were legitimately prescribed the medication.

Also probably **a lot easier** in a sense, looking at **diversion** as the outcome. It's a lot easier than looking at the individual diagnostic bucket.

We can identify **sentinel populations**, where there is high likelihood that the diversion will begin to show up early on.

But – where is the diversion coming from???

Actually - it's not clear that the diversion is coming from people who are prescribed the medicine - that was clear at the FDA meeting as well. No one knows where the diversion is coming from.

So that methodology would work but …

The truth is - we are interested in both sets of outcomes. We are interested in:-

- diversion to people exposed in the community
- and also in how many of the people we expose will develop these problems.

That's the two sides of the picture and it gives you the whole.

B.4.h) How to identify high risk people ???

Most of the studies show that people that do become dependent on prescription opiates had

- a childhood or an adolescent onset of some other kind of substance abuse – they are marijuana abusers, etc. not just users.

So it ought to be possible to pick out people who

- have had these pasts, and who
- will admit to past behaviours and
- don't necessarily think of themselves are particularly vulnerable now.

Such as, for instance, our last two Presidents.

Defining and validating measures of abuse of prescription opioids

There's a paper in press in the Journal of Pain and Symptom Management which describes:-

- the largest study to date trying to define and validate a measure of abuse of prescription opioids.

They've done quite a lot of work.

One of the important questions is **prior history of any drug like that**.

But that's going to be a critical question.

Somehow or another we need to:-

- develop an over-sampling technique
- develop criteria for vulnerability that
- allow us to get a group of patients where these issues are likely enough to occur so that you can ask the questions.

It's interesting that on the one hand –

- we are dealing with a population in the pain setting where 80% of them have a co-morbid psychiatric disease :-
  - often depression, or,
  - anxiety disorder, but
  - not anti-social personality

On the other hand

- **there are a lot of attitudinal and other variables that we don't have a handle on**, on why for some that's a vulnerability factor and for others not. For example:-
  - if they all have depression why do some people start self-medicating and others don't start self-medicating. We don't have a clue about that.

Other possible factors to explore – based on applying lab tests:-

- genetic factors that we need to sort out - in terms of receptors and things like that.
- other kinds of biological markers, or
- neurophysiological markers

B.5. TERMINOLOGY AND SEMANTICS OF PRESCRIPTION OPIOID ABUSE – SOME CONSIDERATIONS (BASED ON JIM ZACNY'S ICE-BREAKER)

B.5.a) Do we all use the same language when using these terms ???

Can we come to a common consensus on what these terms mean ???

We can come to a consensus on what tolerance means i.e.:-

- that you need an increased dose over a time to achieve a given effect and a
- physical dependence is manifested by withdrawal symptomatology

B.5.b) Abuse

Abuse - is an important definition, or term to start off with and it has multiple definitions

The **CSA,** the Controlled Substances Act of 1970 defines abuse as:-

- non-medical use of a drug, period

The Drug Enforcement Administration also uses this as their definition of abuse.

In 1996 a special committee was convened by the Institute of Medicine and they defined abuse as:-

- any harmful use of a drug

The International Classification of Diseases which is a diagnostic criteria instrument formulated by the World Health Organisation, also define abuse as:-

- any harmful use of a drug

DAWN defined it as:-

- non-medical use of a substance for psychic effect, dependence or suicide

Then there's a definition by the APA, American Psychiatric Association - DSM4 -. And that definition, briefly, is

- a mandated pattern of substance (in this case opioid) abuse leading to clinically significant impairment or distress as manifested by one or more of the following occurring within a 12 month period. These are all problem related behaviours that don't just occur once but they occur repeatedly over a fixed period of time.

So can we establish an acceptable common definition of abuse, can we come to a consensus in this room ???

Probably not - because it would probably depends on the question or issue being raised.

For example:-

- if someone interested in a prescription drug, (opioid), is on the street and
- people are using it, and
- people are coming into the ER with drug related problems
- No one is going to care about whether this person meets criteria for DSM4

But

- if a person has problems with these opioids,
- a clinician needs to:-
  - determine the severity of the problem,
    - diagnose it and
    - treat it

And third party payers demand diagnosis with either DSM4 or ICD10.

And then there are **abuse liability studies** – and - how do abuse liability studies define abuse ???

It's somewhat nebulous.

In many cases it's just:-

- a person with a history of using a drug for non-medical purposes and that

- they are currently using that drug.
- So is the situation hopeless? Probably not !!!

B.5.c) Addiction

How about **addiction** - can we all agree on one definition of addiction?

Well, **there are three major well-defined definitions of addiction** and they are as follows:-

Firstly –

- The definition based on a consensus meeting that was held by:-
  - ASAM and the American Pain Society and the
  - American Academy of Pain Medicine, that's one definition that I will describe
- Defines addiction as:-
  - a primary chronic neurobiologic disease:-
    - influenced by a number of factors and
    - characterised by behaviours that include one or more of the listed behaviours such as:-
      - impaired control over drug use
      - compulsive use
      - continued use despite harm and craving.

Secondly …

There's the **dependence syndrome** definition by:-

- DSM4 and there's the
- The International Classification of Diseases (ICD 10)

Both are very similar.

DSM4 doesn't use the term addiction - they use the term substance dependence, and they define substance dependence as a:-

- pattern of substance use leading to:-
  - clinically significant impairment or distress as manifested by:-
    - three or more of the following
    - occurring at anytime in the same 12 month period
    - and they include the criteria of tolerance and withdrawal
    - and then 5 more criteria dealing with really problematic behaviours.

The interesting thing is that:-

- neither **tolerance** nor **physical dependence** are necessary or sufficient to fit this diagnosis. **You have to exhibit a problem related behaviour**. Or you don't have to fit tolerance or withdrawal all together

B.5.d) Do we have a problem here?

The fact that three pain organisations felt that the DSM4 definition doesn't fit when assessing addiction in chronic pain problems, means that yes we have a problem.

The ASAM definition is good.

But in defence of DSM4 - and this is regarding Janssen clinical trials:-

- neither tolerance nor physical dependence is enough to make a diagnosis of substance dependence and
- DSM4 uses formal diagnostic criteria
- does take into account pain patients as acknowledged by the committee who defined addiction in the ASAM, APS, AAPM group

The ASAM definition **is a template still** and they will admit that and the question is:-

- **will the Food and Drug Administration accept Janssen clinical studies, clinical trial studies that use patients defined as addicted by ASAM standards ???.** Nobody knows !!!

And this is a quote from the Journal of Pain and Symptom Management by Sedan Savage:-

> *"If the DSM4 criteria are applied as intended, pain patients using opioids effectively for pain control should not be diagnosed as substance dependent unless patients display maladapted,* ***and that's important****, drug related behaviour and meet criteria other than physical dependence and tolerance."*

So one could argue that -

DSM4 does have a built-in mechanism to discuss chronic pain patients.

B.6. ABUSE LIABILITY STUDIES (BASED ON DON JASINSKI'S ICE-BREAKER PRESENTATION)

B.6.a) Historical perspective

60 years of research in 10 minutes

Historically:-

- this is not a new problem
- the same questions were being asked 100 years ago
- in the USA - there has been a history of opiate abuse and public health and social problems for over 100 years
- definition that was used - comes under social definitions - . i.e. the ability of a drug to create public health and social problems, and morphine created public health and social problems.
- then the issue came in of

Defining what properties of morphine lead to public health and social problems

- number one was that in the certain segment of the population - those people that exhibited drug abuse - was that they would get a certain characteristic objective effect which described the euphoria, i.e.:-
  - they liked it,
  - it was reinforcing,
- number two was that when people took opiate abusers into an institution and they stopped it they saw a withdrawal syndrome which we call physical dependence capacity.
- number three was the public health issue where people died and that was attributed to the respiratory depressant effects of morphine.

So back in the 1920's – there were really two ways to approach this as a problem:-

- one was to find drugs which were selective analgesics which lacked these properties i.e.:-
  - which lacked physical dependence
  - which lacked euphoria.
- the **second** was to take drugs which had a "high abuse potential" (identical to morphine) and make preparations which were less abusable, by, for example, not exceeding certain doses.

Respiratory depression measurement technology was also developed many years ago.

Basically you put people in and you give them carbon dioxide which stimulates respiration and the respiratory centre becomes less sensitive.

You can do very nice quantitative studies with all sorts of measures of this.

Physical dependence – were:-

- developed mainly in the public health hospital Lexington (where Don spent a great proportion of his career)
- using Federal Prisoners who had histories of opiate abuse
- did 3 types of studies:-
  - **direct addiction studies** - take people and just give them the drug chronically and measure withdrawal (and push the dose as much as we could go)
  - **suppression studies** - where somebody would go into withdrawal from morphine and you'd give them the drug and suppress withdrawal, and
  - **substitution** - where you would have them dependent, give them the drug and show that abstinence didn't emerge and that became the - 24 hour short term substitution. The hypothesis was that if a drug was able to substitute and prevent withdrawal and then when you stopped it you had typical withdrawal it too had the same physical dependence capacity

B.6.b) More recent practices

- its changed from prisoners into free-living volunteers,
- no body wants to pay for long term housing people
- you can develop techniques with short term morphine administration and precipitation

It's like the **mouse jump test** but you do it in humans. You put a pellet in the mouse after a day or so you give them naloxone and they precipitate withdrawal.

These are:-

- expensive, and
- they're hard to do, and
- they cost a lot of money
- you really need to know what question you're asking.

What's most commonly done are

- subjective effects of euphoria and
- this came back from the analgesic days going back, t
- this technology is about 60 years old,
- the measures are there,
- the idea is:-
  - single dose,
  - cross-over study,
  - placebo control
  - actually came out of the pain studies which Beecher introduced in studying pain and this then got into the addiction studies
  - there are standard measures, and

- we (Don) probably have data on a hundred to 200 drugs studied this way. (there are something like 10,000 compounds made that have opiate like activity when you look at this)

You can get relative potencies mg for mg.

You can get nice dose related responses.

These studies suggest:-

- the concept that - between the behaviour and the reinforcing effect - the longer you have the less reinforcing it is, the less attractive it is.

Re Liking scores

Even though you get the same sorts of plasma levels - the liking scores may be quite different, which means that:-

- **you really can't predict from pharmacokinetic and plasma levels** what's going to happen.

Data are mainly for stimulants

There are similar data for opiates – but yet unpublished.

B.6.c) fentanyl and naltrexone related comments

Regarding fentanyl - this is from the FDA,

There were two questions:-

- one – **was** extractability**:-**
  - could you extract it and get it from the patch and
- **the other** - was **predicting effects** in certain circumstances (this was with the Duragesic patch) e.g.:-
  - kids putting them in their mouth – and you had deaths
  - also you had deaths when people would put on the patches and get under a heating blanket

This was actually asked about methofenadate.

Don had to design a protocol to measure heat (details as follows):-

- three placebo patches
- three active patches
- a heating pad on two different occasions

It was a lot of work to do this.

It's not clear why:-

- whether this is due to heat affecting the patch making it come out more or
- whether it's to do with the blood flow
- don't know of anybody who has data. – seemed like a clever idea, would be a good way to give drugs. But apparently somebody has published this in the literature and studied this so:-
  - it's not patentable

Don also did - some development work on transdermal naltrexone.

Naltrexone is absorbed.

The idea was:-

- could you get a naltrexone patch (about 25 mg of Naltrexone) that would last for a week
- the problem with researching naltrexone was that:-
  - you can measure plasma levels **but they are extremely low**.
  - It has no agonist effects - all you can study is blockade or antagonism and there are techniques for this
  - In terms of pharmacokinetics levels required for effective blockade – are at the level of almost detectability for naltrexone.
  - there is significant absorption through the skin - which means that
  - if we go to the buccal mucosa it's going to be even greater

B.7. QUALITATIVE OR ETHNOGRAPHIC APPROACHES TO STUDYING OUR POPULATIONS OF INTEREST (BASED ON HARV SIEGAL'S ICE-BREAKER)

B.7.a) What are Ethnographic/Qualitative studies?

Designed to focus on:-

- not only the abusers or people actually in trouble but look also at
- other folk .

Goals of Ethnography

- to penetrate the world of the
  - subject or the
  - population or the
  - people of interest
- to understand
  - how they operate in the world
  - what they do to take care of business
  - whether it involves managing a medical condition such as diabetes and
  - being poor or
  - acquiring and using drugs.

Basically qualitative studies offer:-

- in-depth views
- rich descriptions of target behaviours and
- can help focus and direct quantitative or survey research and
- can assist in the interpretation of quantitative and clinical data.

Qualitative studies - give us some real insight into:-

- who these folk are and
- how they behave and

- more importantly:-
  - what they do on a daily basis and
  - how they make sense out of it

Therefore**, Qualitative Research**:-

- is terribly useful for informing both prevention and intervention related aspects things, and
- can be compelling to a wide audience of both consumers and professionals, if done well

Where does it come from? Anthropology.

Ethnography as a science began at about the turn of the last century.

Anthropologists:-

- went to all sorts of places and
- learned ways of both gathering data but more importantly,
- conceptually organising it
- so we could get a sense of what's going on

Sociologists then applied the same sort of thing to communities within the United States and of course there were European Sociologists who weren't interested in macro-political kinds of things who studied small communities there.

B.7.b) Data collection methods – data triangulation – analytic goals

- key informant interviews – with subjects who have something to tell us about what is going on
- participant research and
- field observations - actually being there and interacting with people and having people explain what they do on a moment by moment basis as it happens; for instance in this kind of research you might have to:-

- go into shooting galleries,
- go into smoke houses,
- hang out on the corner - as deals have been going down and the like.

- focus groups – bringing together either:-
  - active users or
  - other people who have something to say about the phenomenon and
  - asking them:-
    - what do they think - and they actually:-
      - interact and
      - feed off and
      - enhance our understanding of what's going on and finally we can do

- in-depth kinds of interviews in which we can focus in on specific behaviours.

Data triangulation

means that:-

- we don't just accept a single word that
- we look for multiple sources of the data and
- sooner or later enough people independently begin to offer:-
  - the same observations,
  - same perspectives
  - and you say ok this does seem to make sense and it may be real.

Analytic goals - identification and description of behaviour patterns and understanding consistent or reoccurring themes that are there.

B.7.c) History of substance abuse research (qualitative)

Very long history - in fact:-

- in the late 30's Anthony Day studied opium addicts in Chicago and he was talking about some of the so-called opium dens.
- Harvey Finestone in 75 did a study of African-American heroin users.
- Casey set up some of the first actual field stations in New York and they described heroin abuse both on the lower East Side as well as the fashionable South Bronx of New York
- Mike Agar used a lot of the data that he collected from his stint in the Federal Narcotics Hospital in Lexington and told us something about the career of thing.
- Dan Waldorf - same sort of thing careers in dope and that was on the West Coast.
- Harv Siegal hung out in New York City's welfare hotels and learned about vulnerable populations and how things were organised. And
- Bruce Johnson and colleagues took a look at the economics of doing dope on the street.

In the mid-80's - things frankly exploded with the HIV epidemic

All of a sudden the field now began to look at:-

- a whole range of other drugs,
- drug using situations,
- how people were initiated into drugs.

More recently

Focus is on looking at:-

- how people link and engage with treatment
- penetrating and focusing on rural areas (Harv's main area of activity now) and
- demonstrating that these can be successfully penetrated and extensive data collected

B.7.d) Qualitatively focused drug data networks available

Firstly - The 'grand daddy' of these is the **Community Epidemiological Workgroup** which is sponsored by NIDA.

It brings together:-

- drug savvy,
- key informants,
- researchers
- sometimes clinicians

They provide information about what is going on

- in their cities or at least
- their metropolitan areas
- on a national basis.

It has certain strengths:-

- it's what we've got.
- It provides simultaneous reporting.

Some of the **weaknesses** are:-

- the biggest thing is some inconsistency in data and they've had
- significant turnover in some of these key informants which leads to some sorts of problems

Secondly, ONDCP the Office of National Drug Control Policy has done **pulse checks.**

Same sort of thing. There are:-

- 38 sites or so with pulse check and they are
- heavy on law enforcement, national institute on justice, so you'll have stuff like ADM which is Arrestee Drug Monitoring and so on

Thirdly, Harv's Group have put together a Regional Substance Abuse Monitoring Network (SAMN)

- Established a Regional Epidemiologist in
  - each of Ohio's major areas as well as
  - some rural areas and we actually
- Collect information in which they contact active users.
- Use focus groups and other previously mentioned techniques
- Therefore:-
  - gain some sense about the emergence of new drugs,
  - take a look at emerging patterns of concern.
- For instance – they documented and published recently that:-
  - as OxyContin dried up because of the influence of law enforcement, many of the folks who were involved, started to move towards heroin because:-
    - it was more readily available and
    - heroin dealers from the major cities began to penetrate some rural places

Other benefits of SAMN:-

- Get up close and personal with the data
- There is an awful lot of interaction since they're very familiar with their Regional Epidemiologists
- there is consistent reporting and analysis and it is
- highly flexible and
- can focus in on any kind of problem and
- generate information on both licit and illicit drugs.

On the other hand:-

- It tends to be labour intensive,

- it ain't terribly cheap and
- State funding in 2003, not been very generous.

Fourthly, National Pharmaceutical Post-Marketing Surveillance

Privately funded, e.g.:-

- PURDUE (doing of course OxyContin)
- Ortho-McNeil with Tramadol

B.7.e) Conclusions and recommendations for Janssen

What are we looking for and what have we learned?

Obviously research that can:-

- produce valid, reliable and of course compelling data
- Offer real time data collection, analysis and capabilities and
- provide the capability to easily shift focus as targets of interest or
- zero in on geographic hotspots as they are emerging.

What do you need to make all of this happen ??

- feet on the bricks epidemiology,
- assets who are on the ground and can interact with the community of interest. Then you need
- a committee (like this) to help:-
  - interpret,
  - make sense and
  - support the research that's going on.

Recommendations/Guidelines for Janssen

- **Develop a key informant network** to tap into use or non-use by populations of interest. Not only would this necessarily focus on drug abuse researchers but you could actually get very creative and move on

out in a way to tap into different populations and there are methodologies to do this. Certainly there are any number of people that do have experience.

- **Develop a diversion network** which focuses on law enforcement personnel and regulatory personnel so that you have a sense about the data that is beginning to show up there.
- **Focus on ethnographic research** in which you
  - identify sentinel communities or populations or geographic hotspots,
  - establish some kind of ethnographic field stations and be able to monitor these areas prospectively. For instance perhaps the only consistent place that we're discovering some Ultram abuse in Ohio is among so called trend setters and these are:-
    - ***college age people***
    - ***attached to the club and college party scene***
    - ***that are abusing the drug***

These kinds of studies can be readily implemented

B.8. OUTCOME MEASURES IN CLINICAL TRIALS RELEVANT TO ADDICTION TO OPIOIDS IN CHRONIC PAIN PATIENTS (BASED ON BRUCE ROUNSAVILLE'S ICE-BREAKER)

B.8.a) Current practice in substance abuse studies

In the context of - measuring:-

- comparative addiction liability of a new long acting opioid medication in comparison to standard agents for patients with chronic pain
- what kind of things would you measure ???

In substance abuse studies - What we usually typically do is to:-

- take a bunch of people who are
  - already addicted and who want to stop, or
  - who have either stopped or
  - we're trying to get them to stop and so
- most of our measures really are relevant for that sort of a situation

As opposed to:-

- taking a bunch of people and
- you're giving them medication for a particular legitimate problem, chronic pain and then
- our outcome is going to be whether they get into trouble or not

So **what are the outcome domains that we tend to look at as treatment of drug abuse people?**

We can look at things like:-

- high or liking and there are examples of scales the RCI scale, the visual analogue type scales or you can
- measure withdrawal and again there are withdrawal scales. You can
- measure craving and there are a number of craving scales. There are
- misuse behaviours, now this is here we're getting some place and there now are a number of relatively home grown misuse scales. There's no consensus or about what exactly this is, what the thresholds are, there are no norms available but this is really the outcome measure we're looking for. We can
- look at abuse, - a categorical distinction as to whether someone is an abuser or not an abuser. You can
- look at dependence, in several ways:-
  - you can look at dependence severity as a continuous measure how dependent are you, what kind of compulsive behaviours do you have. Or
  - you can look at quantity and frequency….

B.8.b) How relevant/irrelevant are these potential outcome measures?

High pleasurable effects.

Typically this is used in lab studies to evaluate a new agent and one would be interested in whether the new preparation is related to liking or high.

This is not going to be a particularly interesting question as far as our abuse liability is concerned.

It's not going to be any different from the other preparations that have already been studied in this way.

Withdrawal measures,

They are used to evaluate severity of withdrawal symptoms in detoxification studies.

This is only relevant if **discontinuation** is going to be part of the design – somewhat unlikely and undesirable outcome if you are a chronic pain patient

If you wanted to study your agent in an acute pain situation and see if people have more or less trouble going off the medication, that would be another story.

How about **craving measures**? Well they're often used for clinical trials particularly when people have stopped using the drug and then you see if an agent will reduce the craving which hopefully will then reduce their relapse but again - if discontinuation is part of the design of your trial then that's fine.

But, if you're talking about people who might need to be on medications indefinitely or for several years any way a discontinuation is not something that would be a desirable way to use the medication or a clinical outcome.

How about **misuse** measures?

These can be specifically designed for these addiction liability trials **and their applicability for the current study is optimal.**

The draw back is the possible insensitivity and **difficulty in interpreting** varying grades or levels of aberrant behaviour/misuse. For example:-

- for those things that are really **clearly misuse** like forged prescriptions and so forth, everybody could agree that's really misuse – but:-
  - that's not going to happen very frequently in a general population of chronic pain patients
- then there is misuse related to things that people might not want to actually report or admit to – though these have high face validity
- and then there are all these other things that are put on these home grown misuse scales that are milder behaviours that you're likely to see but it's not clear exactly whether that really means anything clinically such as:-

- lost prescriptions or that kind of thing.

Now, what about **abuse**?

Referring to formal abuse as defined by the DSM criterion - the questions would be:-

- are we going to see any incident cases of abuse?.
- Will there be any new abusers that result from this particular trial. You know I think that one of the issues that would certainly be the case is that

if we're going to use formal abuse as a criterion:-

- we have to measure it both before hand (i.e. 'were you abusing before hand') and then
- afterwards – 'have you now developed a new case'.

It would require repeat testing.

Dependence criteria - some of them are relevant some of them won't be relevant.

But if we're again going to look at how many people become dependent on the new medication, -- lets look at some of these criteria:-

- role obligation failure – 'are you going to lose your job' or such things as a result of being on this new preparation. Not very likely. Or:-
  - if you are failing at your job it's because you have this pain condition that's the primary reason
- physically hazardous use - is defined as using during a time when you might be driving and so forth, the problem here is the discrimination ability here - needless to say, being on this long-acting opioid you're going to be

driving and hoping that you're tolerant enough that this isn't going to be hazardous.

- Legal problems - again not terribly likely.
- Social impairment not terribly likely.

So if you're trying to define a clinically relevant syndrome:-

- the applicability for the current study is low but again
- you would need to establish a diagnosis before hand to either rule out people who are already dependent or to make sure that you're not blaming the medication for pre-existing dependence.

Here are some **other dependence diagnostic criteria**:-

- Tolerance - not meaningful - of course they're going to become tolerant on any opioid that they're taking for a long period of time.
- Withdrawal - unless you're planning to withdraw people from the medication as a systematic part of the study - not likely.
- Use more than is intended - that's a potential criterion
- Inability to cut down or stop - again are you trying to cut down, are you planning discontinuation as part of the trial? Don't think so.
- Much time using - again you hope you're trying to use it all the time
- use despite problems or illness - not likely.

And then **dependence severity** is another major outcome that gives us a nice continuous measure of how compulsive the use of a drug is. It is a possible thing to use something like a dependency severity measure but it's made up of those same criteria generally, and symptoms are likely to be probably pretty rare.

Quantity and frequency - , this is a **gold (easy to do) standard** where you would simply look at the quantity of any number of different kinds of drugs. The applicability for the concurrent studies that we'd be looking at would be pretty

high, it's very easy to look at quantity and frequency of different kinds of substance of abuse. There's a timeline follow back calendar where you can get a daily record of what kinds of drugs of various kinds.

One of the things that would be interesting in the current context as well would be

- if people are using the new agent versus a short acting opiate or something like that
- are they more or less likely to use a lot of other substances like:-
  - are they increasing or decreasing their alcohol use, cigarette use etc in addition to the opioids?

B.8.c) Challenges in trying to look at comparative opioid abuse liability

- there's likely to be a fairly low incidence of genuine addictive behaviour such as:-
  - forging prescriptions or
  - getting multiple prescriptions
  - etc.
- So you can:-
  - raise the sample size
  - increase the study duration
  - use lower thresholds
  - over sample for people who are more likely to develop the problems.
- There aren't any validated measures but some seem to be being developed. For example:-
  - one that's being used but hasn't been published yet that Deborah Haller developed to detect:-

  - misuse of pain medicines

- several of the other speakers are doing this kind of work and have their own measures.

So **several misuse instruments:-**

- they would be the key outcome
- most are based on small samples or a single study.
  - the rates of misuse will vary widely depending upon whether:-
  - you're using these low threshold criteria or
  - these high threshold criteria
  - and there are big trade offs in terms of trying to think about a trial whether you want to use a lot of these
    - low threshold criteria which will have nice sensitivity and they may change etc or versus
    - these high threshold criteria

The reason for this is that if we do some kind of a trial where you know you can get nice outcomes:-

- you don't have to have a huge sample size and
- maybe 20-30% of the people will have this as an outcome

BUT - Do you really want to write a paper in which you say on our drug only 15% of the people misuse the drug versus 30% - you know - is this good advertising even if it's significantly better than the other thing???

On the other hand, **if you use these high threshold criteria**:-

- our agent only resulted in 1% misuse versus 4% misuse - then of course your sample size will have to be much larger.

B.8.d) Recommendations to Janssen

- get a pre- and post-treatment diagnosis
- even though you won't see very many incident cases you will at least want to either rule out or see whether the people had a problem before they started.
- over sample for past abusers – in almost all of the studies that look at people who go on to become misusers or abusers:-
  - the vast majority of them actually as teenagers used some other substance or used these substances so that
  - **past behaviour** is generally the best predictor of future behaviour, even if it hasn't been a problem for a while.
- Use:-
  - some kind of a misuse or problem with pain med scale.
  - maybe a craving or desire item or two and
  - quantity and frequency

B.9. OUTCOME MEASURES – RECOMMENDATIONS BASED ON EXTENSIVE CLINICAL TRIALS EXPERIENCE – RELATING TO SUBSTANCE ABUSE IN PAIN POPULATIONS (WORKING PARTICULARLY ON INSTRUMENT DEVELOPMENT). (BASED ON SIMON BUDMAN'S ICE-BREAKER)

B.9.a) Current lack of appropriate instruments

Key factor – as a starting point –

Most of the instruments that currently exist for looking at the misuse or abuse of opioids in pain populations **are pretty poor and poorly developed** and **have not been developed for this particular topic**. Let me talk with you about some of the, what I see as the crucial issues and I want to try and be simple about this because I think that the only way we're going to get some place on this issue is coming at it in the simplest way possible.

Dependence, physical dependence and tolerance are **not** going to be the key issues to look at here.

People are going to have dependence on all opioids.

The issue of **tolerance** is going to be similar for all opioids regardless of delivery system.

People who are taking SSRIs for depression develop **physical dependence** on SSRIs.

If you withdraw somebody from SSRIs quickly you see physical withdrawal and problematic physical withdrawal.

These issues are not terribly important.

With addiction what we're looking at there, is the issue of **being out of control**. Something that is sort of out of the addicts control or seeing what as being important in regard to the issue of addiction. I think that's crucial looking at, to look at that is crucial.

Misuse has more to do with the issue of somehow the person making some sort of decision about using the drugs in a way that the drugs were not prescribed to him or her. So there is more of a **volitional aspect** to this.

Diversion has more to do with the issue of intent - probably criminal intent - if they are being diverted to somebody else rather than the patient for whom they were prescribed. Let me just go back for one second to this.

B.9.b) Recommendations to Janssen

Firstly, use ASI (Addiction Severity Index)

In any study that you do, on the use of or the abuse of opioids in pain settings it's crucially important that a measure that is used is the **addiction severity index (ASI).**

The Addiction Severity Index:-

- is essentially - the coin of the realm in the addictions area.
- Is used probably in 85-90% of outcome studies in the addictions area (conclusion based on a number of studies looking at what measures are used in substance abuse outcome studies).
- Is a crucial measure which provides a of common language to be able to talk to people and enable them to understand and interpret what you're doing in other areas.
- Contains – mostly - measures pertaining to addiction rather than misuse or diversion.

You **may have to make some modifications** on the Addiction Severity Index.

it was developed in 1980 by Tom McKellen from Upenn,

it is used with extreme frequency.

Variety of problems with the delivery of the addiction severity index in terms of reliability of raters.

It's an **interview form** and is done:-

- to identify the population,
- look at the population as well
- as an outcome measure.

This problem has been approached by developing a technology based administration of the ASI.

The ASI is a **measure which must be used,** in any study that you do of addiction with opioids.

Secondly, you've got to work with substance abusers in a substance abuse population

This is **Crucially important** in looking at the opioid liability of your product i.e. to work with an **enriched population**.

If you're looking at a pain clinic population:-

- base rates are going to bite you in the behind and
- it's going to be a very difficult thing to do.

If you look in a substance abuse treatment centre:-

- we know that a **large and significant percentage of substance abusers also have chronic pain problems** and
- one of the studies that you do must be in a substance abuse treatment setting with pain patients within that setting

Another **advantage** of working with a substance abuse population:-

- it's much easier in a clinical trial to follow people up in an addiction population.
  - Simon's group recently did a study on a certain aspect of medical care where they had a 90% follow-up rate. You're not going to have a 90% follow-up rate with these folks in this kind of study. If you can achieve a 70%, 60% follow-up rate you're going to be very, very lucky indeed

Possible concern – about patient honesty

You may have concerns about patient honesty and whether are going to really tell you that:-

- they are abusing or misusing the drug.

In reality there are some very, very surprising findings in which people will tell us (Simon's experience) on a questionnaire that:-

- they are getting opioid medication from more than one physician. People have said that they are doing that.
- Even if you start by asking people a yes no question about that – you will find - that sometimes people will write on the side of the paper, but
- If you put together a 5 point scale you'll get plenty of people who indicate that they participate in these behaviours - much to one's surprise.

Also - You need to be aware of all the co-morbid conditions that these patients will have.

Thirdly, you need to develop psychometric measures

Because:-

- the measures are lacking - there aren't good measures in this area – this is very surprising !!!
- you are going to need to do measurement development
- the history of psychometric measurement development in the area of opioid abuse in pain populations is very, very poor.
- Interesting to consider a measure that would be able to predict or would look at the issue of prediction of:-
  - who would misuse opioid in pain settings
- Simon is developing - with support from NIDA - a **screening tool** to do just that and. called a **SOAPP** tool which is the **Screener and Opioid Assessment for Patients in Pain** which would:-
  - have good psychometric properties
  - be able to do better at helping clinicians to determine – amongst the patients they're seeing:-
    - which ones might have more difficulties in regard to using opioid medications and
    - which would probably have fewer difficulties in that regard
    - though it would not be able to fully predict - obviously there are issues of sensitivity and specificity
- the best measure at this point from a psychometric perspective is a measure that was developed by Peggy Compton which:-
  - is an interview and that measure

- was developed with 44 patients - that's the basic scale - the **gold standard i**n this area is a measure **developed with 44 patients** which is pretty bad.

The process adopted in development of SOAPP

Started this development with something called **concept mapping**.

Several KOLs in this Ad Board actually took part in this concept mapping processes.

B.9.c) Concept mapping

- is a way to take a series of concepts and
- get some consensus from experts as to which concepts are central.
- allows you to look at various kinds of concepts from different stakeholder perspectives. On many of these concepts what's important to different stakeholders varies greatly. What's important to
  - a surgeon - maybe different from what's important to
  - a surgical patient.
  - what we see with this issue of opioid abuse is that there is a great deal of consistency, there's an R of 0.99 amongst our doctor level participants and non-doctor level participants. People mostly see these concepts in a similar kind of way and what's important in a similar kind of way.

In relation to **opioid risk or liability of different patients** what Experts say is **centrally important** in regard to patients who will likely abuse or misuse opioids:-

- is represented by islands on a diagram/chart and t
- the islands that are sort of higher than others are the ones that experts see as most important in terms of that issue
- many of the concepts that people have been talking about today and bringing up today are represented in these diagrams

The next step - again with NIDA support - is:-

- to do a large trial looking at:-
  - the way that SOAPP predicts how people will be using their opioids 3 and 6 months hence and
  - this scale will be as rated by the Compton interview. This scale will have some place, we're not completed we've not finished it yet.
  - this scale (not completed yet) will have somewhere between 25 and 50 items that can be self-rated by the patient and hopefully:-
    - be predictive of their future use or misuse of the opioid

What have we found out so far ? (in developing SOAPP)

- interestingly - an initial version of the SOAP tool was far better at predicting misuse than were physicians in a specialty pain clinic.
- So, the correlations between ratings on the SOAP were better than what specialty physicians were doing in a pain setting.

B.10. IMPACT OF FORMULATION ON ABUSE LIABILITY (BASED ON TOM KOSTEN'S ICE-BREAKER)

B.10.a) Regarding patches …

- the sense overall is that they are **minimally reinforcing**
- the onset of them is too slow
- Lots of data on **stimulants -** you put them in a patch, you don't abuse that stuff

It's really all about extracting it out of the patch **and 50-70% of the opiate is typically left in these patches**, whatever the patches are. So there's a lot of drug that's still there even when you throw it away.

So that's one of the risks that's inherent to this.

What are the street chemists likely to do ?

You ought to test in your own laboratory before they test it out in their laboratory:-

- is it a better matrix,
- proves easy to remove for
  - intravenous injection
  - oral ingestion or
  - smoking and

Tom Kosten's sense of what he's seen of this patch is the answer is yes.

You've got the drug right there and you've got the naltrexone underneath it. It's probably not going to take rocket science to get it out.

Can it be extracted by weak gases like vinegar, salt solutions, even toluene – these have commonly been used before and they'll figure out how to do it again.

And again if there's just a differential solubility between your fentanyl and the naltrexone, whatever it is, that will simply separate the things out.

B.10.b) Regarding studies

So what studies do you want to do?

There's a whole issue of drug and alcohol dependence which everybody is familiar with that goes to this.

What are some of the essence of those articles?

The **real world clinical epidemiological data** carry a lot more weight than numeral-laboratory data in the FDA assessments of abuse liability.

You can do all the animal studies and human laboratory studies you want, they are generally not that impressed with them.

Opioid abuse is much more valid than studies in healthy normals.

What's missing in clinical trials?

Kathleen Brady in her article describes these rather nicely.

There's generally:-

- no **drug discontinuation syndromes** described in the clinical trials that are done
- no **assessment of drug liking** when clinical trials are done of most of these medications and they
- **exclude potential abusers** as subjects with many of these studies

3 kinds of studies you might want to do

- human laboratory studies, liking studies comparing different formulations, this ones a slam dunk if you want to do it and compare:-
  - oral to transdermal to IV and
  - you'll show that – transdermal - people don't like it at- . A great study to do if you want to show it's not re-enforcing.
- Out-patient clinical trial:-

- George Bigelow did some nice clever designs of how to look at this with the anorectic agents. But with different formulations:-
  - you need a double dummy formulation so
    - everybody gets a patch - some will be real, some will not be real,
    - everybody gets a pill, some real, some not real, based on your placebo control.

- Epidemiological studies – you obviously have experience with this with tramadol and it's worth reviewing that again. What's the expected outcome:-
  - relatively low liking of the transdermal formulation
  - extra use or diversion of the transdermal is going to be minimal compared to the oral formulations - that's generally what you'd like to see as an outcome and it's the kind of outcome you could expect.

Reference to Bayland's study:-

- in the Journal of Clinical Psychopharmacology
- these were non-dependent opioid users
- it was done with Ed Sellers up in Canada
- he administered three formulations so you could look at is oral, IV, transdermal and:-
  - ask the subjective responses, you could
  - examine dose response
  - look at the tail time course.

The Bayland study was interesting – what they did is

- look at the time course of fentanyl vs. another derivative of fentanyl which
- showed a somewhat slower onset for this other derivative of fentanyl and they
- suggest that this may make it having a lower abuse liability issue than fentanyl itself

So that's obviously something the company could think about.

May be don't put fentanyl in it. Allow self-administration vs. money after initial exposure.

Comparisons of transdermal formulations

You could

- compare it to some other one that you think is more abusable
  - may be transdermal morphine. But
  - NOT transdermal buprenorphine obviously, since you are going to lose in that comparison.

Out-patient clinical trial

Again:-

- based on the stuff that Bigelow did - published back in 1980.
- looking at agents to treat weight gain essentially
- the parallel study would be opiate dependent out patients
  - use it as a substitution agent after stabilising everybody on something like a low dose of methadone, 60 milligrams, then
  - shift them to an equivalent dosage of your transdermal vs. an oral formulation - your blinded double dummy procedure.
  - allow extra medication for daily take homes and
  - then see what happens i.e.:-
    - Do they return all the medication,
    - do they use it all up,
    - do they use the extra stuff you give them,
    - how well do they stay in treatment,
    - do they like keep coming back to get more stuff or not,
    - what's their positive and negative subjective reports?

These would give you quite direct behavioural data about just how abusable are the different formulations of it.

But, right now it looks like you don't have much of a problem with fentanyl .

B.10.c) Validation of outcome measures that could potentially be used in Janssen studies

With reference to Bigelow's study …

In a study modelled on the Bigelow study, i.e. a study of various kinds of opioids, the outcome measures of the trials would be things related to misuse or how many pills came back etc – the question is:-

- what's the status of the validation of those outcome measures in this population or in any population?

Answer - non-existent.

But - you'd be

- doing a tremendously creative study that follows one that's been done 25 years ago and
- breaking new ground in a way that
  - on the one hand might be totally stupid to waste your money on,
  - on the other hand it's an interesting idea

Alternatively, could pursue that in a serious way by validating outcome measures.

This would not be something you'd do over night.

Conceptually this would be a **tremendous potential contribution to the field.**

You could run it against a number of drugs and you'd **develop a new standard for the field** but it's not simple to do.

B.10.d) What are we really measuring???

Are there 2 different addiction paradigms:-

- **one related to socio-pathic personality and**

- **the other not related to socio-pathic personality– e.g. related to pain patients**
- **supported by the concept of 'negative' and 'positive' euphoria???**
- **And are we therefore measuring different things in these 2 different** scenarios???

We're talking about **pain clinics** but most of our data comes from what you would call the **anti-social personality disorder**.

Back in the 1920's one of the great geniuses in the area **Larry Cobb senior** who was basically looking at the addiction problem, would go round the country talking about the addiction problem, and he talked about two patterns:-

- one was **negative euphoria,**
- the other was **positive euphoria**

He said that what you were measuring

- in certain sorts of people was essentially **elevation of mood** - people who were taking this for what you might call a recreational use, versus
- another part of the population who is taking drugs **to suppress ongoing dyseuphoric symptoms** whether they come from depression or anxiety etc and this transcends a lot of particular drug use

So when you look at clinics and populations you're going to study – it is very critical to consider:-

- whether the measures we've **developed for the addict sociopath** are applicable to the other – non-sociopath - kind of population.

B.10.e) Most appropriate Outcome measures when testing for the 'abuse-protective' effect of adding Naltrexone

What should we be looking for:-

- misuse
- abuse
- diversion

- addiction

it's very unlikely that naltrexone will have any effect on misuse because

- that's not the issue for the person who's misusing it.

Naltrexone will **probably have some affect on diversion** or presumably could have some affect on diversion because:-

- when it gets out on the street they're not going to like it unless they extract it very easily.

So that would be a study:-

- to design a study to look at naltrexone plus fentanyl in a transdermal formulation with the **primary outcome of interest being diversion capacity**.

It's a totally different kind of study than to think about looking at **misuse** or **addiction liability**.

You want to certainly design studies - **the way a lawyer goes to a court case**.

He never asks the question that he doesn't know the answer to already.

You want to be very clear what the answer is you're expecting already.

So there are three types of potential studies for Janssen to consider:-

- some that you can design here where you can get very clear expectations of what those answers are - and then you go with them.
- other studies where it may not be so clear and
- other studies where you can just totally waste your time because the question is not worth answering

Note, however - that

- if studies were done to demonstrate that

- **transdermal administration was less likely to be misused or abused in the clinic** setting, that would be a very valuable study for clinicians

It's **surprising it hasn't been done**. It's been done with the stimulants. Don's got some nice data and the data are **overwhelming** that **you hit a slam dunk with it pretty much with opiates too,** just the epidemiological data would suggest that if nothing else - do it.

B.11. RISK MANAGEMENT (BASED ON JACK HENNINGFIELD'S ICE-BREAKER)

B.11.a) Preliminary comments

What we've got to do is look at the different populations:-

- the patient population,
- people who abuse drugs and
- people who divert drugs who
  - may or may not abuse them but
  - may find the drug attractive.

Where is the FDA coming from on this

They've done a couple of position papers:-

- one is looking at risk assessment and what they're saying is let's:-
  - identify,
  - estimate and
  - evaluate
  - **possible risks and potential risks**

B.11.b) What is Risk Management

Risk management. - What's that?

It's the - overall and continuing process of minimising risks throughout the life cycle of the drug including reserving the option to go back and fix things.

Risk management programme –

is a **strategic safety programme** that's supposed to cover all these populations.

So**, it's much more than abuse liability.**

It's things like safety purse and that gets integrated into all of this.

Mark McClellan the new FDA commissioner has stated several times and it's on the FDA website that:-

- risk management is a major FDA strategic initiative.

So how do you do this and how do you balance it all?

Beyond Controlled Substance scheduling - is where we are being asked to go.

Keep in mind that Controlled Substance Act

- wasn't really designed with formulation in mind.
- It was **chemical entity** focused - and here
- we're looking at **chemical entities in lots of different formulations and under different conditions**

Years ago FDA would say well the population and indication doesn't matter.

It matters big time in risk management..

Jack has looked at **probably 10 different formulations of nicotine**.

The formulation matters.

Now the FDA response to this has been emerging over the 1990s and it's included looking at drugs like Acutane the acne medication - could lead to depression and suicide.

Oxycontin in the area of drugs with abuse potential just blew the lid off.

And it was a couple of years ago, that Cynthia McCormick stated in the New York Times:-

- "*We didn't appreciate the formulation was so important we'll never let that happen again".*

So

- FDA is using this to supplement scheduling and
- DEA staff are working with them - and DEA has quite a staff and some people that are quite knowledgeable

B.11.c) How do you go about it? What's the data set?

- Abuse liability testing is one of the corner stones - of course you have to have to have that but that's really limited.
- you need ethnography,
- you need qualitative studies,
- you should maybe explore getting your market research people involved. Market research used to be an oxymoron but you need to know:-
  - how people use,
  - under what conditions they are attracted, etc like the conditions under which all of a sudden heroin came to areas where it wasn't, when Oxycontin was driven out.

And risk management gets into things way beyond traditional abuse liability scheduling and testing and it's intended to supplement scheduling.

The abuse liability of fentanyl is a given - it may very well be worth doing the kind of obvious study of comparing the patch formulation. But it's not going to go very far in helping FDA design your risk management programme because they are going to say that's assumed.

They're going to be looking at

- the chemistry.
  - Economic factors and
  - competitive drugs,
  - what are factors that influence safety:-
- the fact that it may be safer when swallowed - that's a factor that fits into the risk management programme

B.11.d) Potential risks

Risk management programme can limit market potential as seriously as Controlled Substance Act scheduling

And depending on the risk management programme:-

- it can make it difficult for patients to get access – sometimes it is so draconian that Companies wonder should they even bother to go forward

In the absence of a credible sponsor proposal the FDA and DEA will come up with something.

One of the problems is that they are saying that this is science based and want it to be science based – but - there isn't much science.

This is seat of our pants at this point. It's what makes sense and this is where perhaps the ethnography kind of research and qualitative research can at least:-

- give us a step forward and
- give us some rationale of what we're doing

For example **regarding naltrexone**

- a lot of us believe that a lot of drug abusers think naltrexone is a kind of a dirty word
- Is that true?
- You've got a bunch of people in this room that know something about that but
- **what we know or say isn't really good enough**
- maybe **you should be doing ethnography and market research in drug abusers** and finding out what they think:-
  - Is this a deterrent? - That might give you some data

B.11.e) Practical Steps – Basic elements of Risk Management

Bottom line:-

- go to the FDA websites
- look at what's been done recently.

- the bottom line is - the sky is the limit.
- The ACTIQ programme - Cynthia McCormick mentioned in one hearing, or maybe it was after the hearing, she said:-
  - *"You know - basically what we did was we got together all the ideas that came out of the advisory hearing, made a list and just picked and applied them. And so that's how you got this bizarre thing and you need fanny packs and take home boxes and all this stuff. Most of that was driven by the safety concerns in children, and not abuse liability. But abuse liability was a factor too."*

It's much more complex than just abuse liability.

But we have some relatively recent examples that are worth looking at and you haven't attended the hearings it's worth looking at the web cast and documents.

It's way beyond chemical entity now.

B.11.f) The wild cards …..

- FDA's risk aversion versus patient access
- You're pinning your hopes on which staff are kind of leading the charge, you've got a different balance:-
  - McKellan seems to be stressing patient – hopefully he will maintain that.
- We don't have FDA guidance for abuse liability testing for more than 3 years
- How RMP relates to CSA provisions is basically evolving per drug.
- The advisory committees including the safety and risk management committee have relatively little experience in this area:-
  - The drug abuse advisory committee that gave us some basis for what the rules were and how they work has been gone for several years now.

- Break throughs in street chemistry, - it's chilling when you go to some of the internet sites and just see - within 5 minutes after the drug is out people will be telling:-
  - how to defeat it
  - what to do and
  - is it worth the hassle

So you have to find out

- not just **can you defeat it** but
- **how defeatable** is it**,**
- how easy,
- you're getting into behavioural economics - Headline news drives FDA

B.11.g) The need to develop a good rationale

Moving forward? - Must develop an argument for the rationale …

You have to identify all conceivable concerns.

Everything fair game no matter how trivial and then some.

What comes out of the ethnography studies – could be very helpful

- Conducting studies to address key formulations will be important
- . I mean knowing the formulation it was interesting

And in some cases:-

- it's not studies
- it's a rationale argument based on what experts including drug abusers tell you

B.11.h) Packaging the information/data set

How you package this and quantify this is a real challenge.

At the palladone hearings a couple of weeks ago:-

- they handled this not in the public hearing, and
- apparently that was by agreement with FDA staff
- that they talk about all the different ways so as not to give the recipe, and make it easy.
- And here it's a real balancing act, because:-
  - the group of the FDA which is focussing on the patient might say well we want you to put the formula in the labelling so people will know not what to do. Well that,
  - while the other group of the FDA is saying well hide it, we don't want anybody to know
  - This is going to be challenging

And then **looking at risk management proposals that have been developed:-**

- some of them have rationale,
- some of them have a little bit of science and
- you're going to have to look at this formulation and put together something that appears rational

In dealings with the FDA and DEA…

- you could sit back and be a follower and let FDA and DEA come up with your risk management programme because that's where the action is going to
- Or take control of your own destiny and become a leader in this area.

It is **critical to think:-**

- not just of this product but
- coming up with something that **also suits your product pipeline** because:-

- it would be real easy to come up with something that fits this particular product and is inconsistent with other products including your own products in the pipeline and
  - FDA is not going to be focussed on that. They are going to be focused on this product.

B.12. CLANDESTINE DRUG LABORATORIES (STREET LABS – KITCHEN CHEMISTRY) (BASED ON BOB BIANCHI'S ICE-BREAKER)

B.12.a) Categorization of Labs by DEA

DEA like to divide these labs up into three different categories:-

- **the highest level** are the ones:-
  - that have professional chemists on staff and interesting that:-
- the **largest fentanyl laboratory** seized in the country was seized in the mid-80s at a university in Pennsylvania. One of the professors needed to supplement his income.
- **Organised crime** is another area. They:-
  - provide a lot of money, protection and
  - very commonly the space that they occupy is a commercial laboratory or commercial size equipment that can make:-
    - kilos of material as well as make
    - millions of tablets - as they do with ecstasy
  - purchase their chemicals from legitimate sources very frequently and
  - just divert them into these illicit activities. In many cases
  - they have intrusion detection systems and
  - some safety considerations as basic as a fire extinguisher but in some there are no such things.

In fact:-

- many of the labs that are seized are seized as a result of a call to the fire department. The fire department shows up and they see a building ablaze and they find glassware and solvents, ether in particular that's very flammable and are feeding the fire. And these people have the capacity to make just about anything such as:-
  - methylamphetamine and amphetamine which are very easy
  - LSD and fentanyl are not so easy

- THC is another one but we don't see very much synthetic THC coming out of clandestine labs.

The lowest level

we have to keep in mind that the people that operate these labs:-

- are not stupid
- they maybe uneducated but they
- are very brilliant and they
- know how to do these things
- they know how to not only make illicit drugs but
- to extract them from different matrixes
- and the outlaw motor cycle gangs have
  - put methamphetamine on the map,
  - methamphetamine is our number one illicit drug in the United States and
  - these operations can be done just about any place. Some of the problems with the smells that are emitted will sometime alert somebody that there is illegal activity going on - but in many cases nobody really knows

Whatever you find in a kitchen can work as laboratory equipment:-

- pots and pans, stirrers, measuring cups,
- scales that you would use to weigh out different types of food

The underground is very, very active in providing chemicals and supplies.

On of the things the DEA has set up is:-

- **sting operations** where they pose as a supplier for chemicals and precursors and just watch the bad guys come in and place their orders, it's easy from there

There's also a **very active publication activity** in the underground where there are books published that will tell you:-

- how to make clandestine drugs and
- how to use them

The internet is another resource, and these people are most frequently dealing with the simpler types of drugs.

And the lowest levels in many cases is the user that might be doing something that somebody else told them to do:-

- this is how you do it,
- you just pass down the formula from person to person
- so they learn how to do things like cut drugs for example.

The operation that you may have seen on TV with playing cards is a very, very detailed skilled science on how to air those and then mix up the entire batch so that you've got a uniform distribution of heroin throughout and people in those positions are coveted in the clandestine world.

Over 8,000 methamphetamine labs were seized in 2001 and not

- the concentration and the focus in California, and
- there's an infusion coming from Mexico up into the West and South West.
- that represents more than half of the labs that were seized.

The total number of labs includes where a seizure is made and they find:-

- nothing but a boxed up laboratory waiting to be set up,
- there's no activity going on,
- no drugs being made and of course
- the dump sites where they have to get rid of all the residuals from their processes

The DEA has taken on the responsibility to clean up these labs so that if there's a lab any place in the country:-

- the local police will call the DEA and say come on down guys and clean it up and
- a lot of money has been spent over the years in just cleaning up these toxic dump sites so
- this is a very active activity. And although most of the operations are making illicit drugs, every one of those three labs has the capability to extract controlled substances.

B.12.b) NFLIS (National Forensic Laboratory Information System)

Is a group made up of 187 crime laboratories throughout the country reporting to the DEA what substances they are finding.

The reason the DEA did that was because the level of investigation for the DEA was so high at national distribution levels and international distribution we never really knew what was going on on the street.

So accessing what the State local crime labs was a formidable task, it was tried several times unsuccessfully but very recently they did manage to get co-operation because this required some resources that most crime labs don't have to collect this data.

Of greater interest to us:-

- narcotic analgesics, fentanyl is number 12 at .3% of the total and - as we've heard before - is it really a problem???

B.12.c) The scheduling criteria used by DEA

When DEA is scheduling drugs the things they look at include:-

- the abuse potential and
- the extraction of the psychoactive substance from the dosage forms – this is something of great concern. **If it can easily be isolated it can be easily abused**

There are other issues that come into place as to whether or not it is abused but the ease of extraction is something the DEA looks at and something that we're going to have to look at as well.

This is frequently referred to as reverse engineering and this patch is a classic example.

The Crime Lab would look at the patch and literally try to take it apart, try to figure out what makes it work.

There are basically two criteria:-

- **firstly,** we look at the **physical properties:-**
  - can we peel the patch apart
  - are there particles that are visible either to the naked eye or microscopically that can be separated out
  - Is there something unusual about the antagonist or the active drug that will allow us to do a physical extraction and
- **secondly**, we look at the chemical properties:-
  - can we extract them? And we know,
  - intuitively we know that this can be done because:-
    - in the Janssen quality control laboratories they do extract this substance, separate it from naltrexone so we need to demonstrate to the DEA that***:-***
      - we have done an exhaustive study of this and
      - recognised what the short comings are and
      - make certain that whatever is presented is not something that the DEA could find contrary information about

B.12.d) Labs that are extracting Controlled substances

There is no published data on the laboratories that are extracting controlled substances.

From experience over the years we've seen that taking place but:-

- no one has ever collected that data,
- how many labs are extracting controlled substances

Each of the 3 levels of laboratories can do some element of the extraction of course the more difficult ones would be in the higher class labs.

B.12.e) Current DEA thinking about abuse deterrence

Current DEA thinking is - perhaps the pharmaceutical industry should be looking at unique types of delivery systems that:-

- would preclude abuse that
- would make it very difficult,

Certainly nothing is going to be 100% foolproof but we need to look at that as part of our development in R&D to find things that will prevent people from using the drugs which they were not intended to.

B.13. DEA'S REGULATORY ROLE (BASED ON JOHN COLEMAN'S ICE-BREAKER)

B.13.a) Primary responsibility of DEA

DEA's regulatory role - Begins with the Controlled Substances Act

The DEA:-

- has the primary responsibility for enforcing that Act including the Civil or State provisions that regulate the controlled substances.
- provides a closed system for doing so, so that:-
  - controlled substances/drugs:-
    - are tracked very, very closely and carefully by the Federal Government
    - from the point of manufacture
    - right down to the end user at the pharmacy or the hospital

DEA and FDA share responsibility for scheduling these drugs based on their potential for abuse.

Strategic sources that the DEA uses to understand and hopefully to allocate and target resources.

When they go to Congress for appropriations each year:-

- they have to justify the money they're asking for certain programmes and
- they do that by using some strategic processes that allow them to give a sort of prognostication of the parameters of the problem.
- ARCOS is a very important one.
- DAWN is also very important as well and so is
- NFLIS
- all three of these are somewhat different but they all sort of dovetail into what the government is trying to say strategically in terms of the threat of drug abuse

B.13.b) ARCOS data

Interesting to see that Anchorage was number one in the United States in terms of its cumulative distribution of OxyCodone.

Now before you draw any major conclusions Missouri was number two.

Half the population of Alaska is under that age of 30,

690,000 people up there, not too many people retire to Alaska so we can't really say that the volume of controlled substances is based on the number of chronic pain patients or end of life situations in Alaska.

B.13.c) DAWN data

Some very interesting numbers pop out of there.

The individual frequencies of mention in the DAWN database for the specific opioid for the year indicated from 1996 to 2002. Show them moving in different directions, usually upwards, some of these drugs have quite different profiles than others.

Potential problem – in tracking by formulation

DAWN tracks drugs by form and one of the problems is transdermal is going to be transdermal. So we have fentanyl transdermal in DAWN we'll no longer be able to say it is Duragesic**.**

So DAWN based study then would not be a study that could discriminate the abuse liability of those drugs.

B.13.d) NFLIS Data –

NFLIS data are used to:-

- support drug scheduling efforts as well as
- to inform drug policy and drug enforcement initiatives.

So we're looking at so many different angles here at the same time that we need to keep track of them all.

NFLIS data with respect to the opioids

Quite interesting because:-

- two non-controlled substances actually come in above a controlled substance.
- one of those non-controlled substances is Tramadol which is
- non-controlled in good measure because of the important risk management plan that was submitted by the company when the applications for a new drug approval was requested from the FDA

B.13.e) Tactical information that the DEA uses to focus its resources

- complaints from the outside
  - from State and
  - local folks from
  - members of the medical and regulatory communities as well as
  - the public.
  - Criminal cases – which generally generate additional criminal cases so they sometimes have a self generating capacity involving:-
    - Informants and
    - co-operating witnesses,
    - people who just call up and say here's what I know and here's what I want to do

B.13.f) % of doctors responsible for diversion or leakage

What's the percentage or number of doctors responsible for the diversion of drugs or the leakage of drugs from legitimate channels into the illicit traffic

- AMA and DEA have estimated that

- 1½-2% of physicians are dishonest and perhaps
- another 5% are negligent at prescribing practices and there are about
- a million DEA practitioner registrants - these are physicians that are registered by DEA to be able to prescribe Controlled Substances
- so that would give us approximately **70,000 registrant physicians** maybe either:-
  - dishonest and/or
  - negligent in prescribing practices

Even though that percentage number is relatively small, that number could be very important.

As Congressman Rogers indicated:-

- just a couple of doctors in his State, Kentucky, were responsible over a relatively short period of time for "millions of doses of controlled substances hitting the streets" so even though we're talking about very small numbers we're talking potentially very large impact.

We need to:-

- develop and provide materials by the speakers bureau as well as the Janssen reps and the other folks who will be out there actually representing this product to the practitioners
- conduct phase IV trials of product in co-operation with pain doctors who also treat or perhaps addictionologists as well as pain doctors because they see both sides of this sort of spectrum and
  - they have a very good appreciation for a lot of the issues that we're talking about here today.
  - conduct liking studies which are very important. We perhaps didn't think so some time ago but now we're looking at some of these issues - liking studies will become far more important than we previously thought

B.14. FDA PERSPECTIVES ON ABUSE LIABILITY (BASED ON NAT KATZ'S ICE-BREAKER)

B.14.a) Don't let FDA drive research agenda

It's **dangerous to let the FDA drive any scientific research agenda** for two reasons:-

- first of all the FDA doesn't want to drive anyone's research agenda
  - they want themselves to be driven by what's the state of the art in the medical community and not overly constrain development of more creative or superior methods for studying various phenomenona
- second - is that it's **very difficult to guess what's the FDA's thinking at any point in time** so:-
  - it's better to just do the right thing as well as you can while trying at the same time to be mindful of how one will interact and communicate with the FDA around these issues

The FDA:-

- expects the experts to lead the way and are
- watching and waiting to hear from people what they should actually be providing.
- Do view themselves as having a mandate to protect the public health in general, even beyond the specific safety and efficacy of any one particular drug so that is part of their concern
- is not just a monolithic organisation:-
  - there are divergent constituencies within the FDA depending upon not only:-
    - their own personalities and
    - where within FDA they sit but also
    - to what extent they have relationships with DEA and with other entities that also have interest in these areas

- so to say that there is one perspective on this within FDA is to obscure a more complicated situation

The Controlled Substances staff right now is considering guidelines for:-

- what evidence is required to produce labelling around the issue of relative abuse liability.
- guidelines expected to come out within the next year which usually means within the next 3-4

B.14.b) Current evidence on relative abuse liability

People at FDA respect the fact that right now **there's not a lot of evidence either way on the relative abuse liability of anything in the opioid arena**.

They accept that

- there's a lot of tradition and certainly
- there's been a lot of work done over the last 60 years to:-
  - modify certain aspects of the abuse liability testing paradigm
- BUT – overall - it's almost like a blank slate

When talking about abuse of modified release opioid we're really talking about several different populations of interest:-

- the patients that we prescribe these medications to - what percentage of people prescribed these drugs:-
  - develop a new problem,
  - redevelop an old problem

Complications of therapy is an area that the FDA has a long standing and indisputably legitimate interest in and here there is essentially no data here.

- **the public at large** - the people in the community who may obtain these medications from:-
  - diversion or
  - synthesis or

- other sources that the FDA has in recent months more vocally justified why it's ok for the FDA to be interested in this problem.

- **Collaterals** - You know:-
  - you're 70 years old,
  - you have cancer,
  - you're getting OxyContin,
  - your 18 year old son is taking half your supply and going out abusing it with his friends at parties

So the FDA is interested in all these three groups.

What studies would constitute evidence for differential abuse liability of a modified release opioid? (as viewed by some at the FDA)?

B.14.c) Liking studies

They certainly have a great deal of respect for the traditional liking paradigm developed by Dr Jasinski and others. However, one key issue to them is

- what population are you studying in those paradigms?
- is it just people who are addicts? –
  - probably substance abuser often with anti-social personality disorders
  - certainly that's the traditional population and I think
- there's a view at the FDA now that:-
  - we need to know whether that's relevant to the patients that we're prescribing these medications to, and
  - if those patient populations are not necessarily relevant to pain patients then we need to study pain patients

B.14.d) Development of innovative Outcome measures

What outcome measures in terms of these liking studies would be most relevant if we're talking about studying patients with pain as opposed to the typical patient that has been studied?

When testing patients with pain or without pain:-

- **comparators should be tested at equal analgesic doses** and perhaps they had seen some studies that they were very sceptical about where:-
  - people set up straw men with too low doses or
  - too high doses
  - that were not really relevant,
  - they were not really comparable to each other

B.14.e) Pharmaceutical studies

We know how easily the formulation is violated.

The heating pad issues, how easy it is to separate antagonists.

They are very interested in knowing

- what's the standard of practice in the community
- based on internet and other sources of information
- in terms of how easy these things are to compromise.

B.14.f) Collateral abuse is very important to them

How is the medication secured in the household.

We all are aware of the ACTIQ risk prevention programme where:-

- there was a big song and dance made about how it's stored
- and that it's locked
- and you have to get this kit and all that kind of thing

So how it's secured in the household is an important issue for them in terms of abuse or misuse liability maybe.

Data on abuse or misuse by collaterals by household members.

Also very interesting to them – but, they have no idea how to do that.

They've never seen any examples of doing that but they are interested in people developing methodologies even if it's just qualitative studies to look at:-

- how people in the household get the drugs
- what their relationship is with these medications

B.14.g) Counting dosage units

How many dosage units are needed is actually a very important question to them. If you get a prescription of OxyContin:-

- you've got a bottle of 300 dosage units that's 300 potential events, which is
- different than if you've got 15 patches that you can't really in any easy way subdivide into different dosage units – which represents 15 potential events

B.14.h) Clinical trials

They had some thoughts about that.

They felt that a well done trial with:-

- validated outcome measures,
- with a clearly defined patient population,
- comparing different modified release opioids
- would be of extremely high value
- maybe even a gold standard would not be an exaggeration.

Concern about comparing things that are comparable.

Need for a **clear and validated construct.**

You have to **know what you're measuring** and it needs to make sense **.**

You have to be able to **measure it in a validated way.**

So that **the conclusions can be reliable**

- Therefore, this study couldn't be started tomorrow it would have to be part of a research programme in which;
  - these constructs are validated and
  - the measures to measure those constructs are

B.14.i) Population data

They're interested in:-

- doctor shopping

But they had not really thought a lot about the:-

- potential usefulness of monitoring either:-
  - prescription monitoring programme data or
  - claims data from other sources

There are

- **tremendously rich databases** that are
- being collected by multiple States in the United States**:-**
  - something like 19 have electronic prescription monitoring programmes
  - three of whom have proactive programmes to communicate with physicians
- Then there's **Medicaid** which has **tremendously rich claims database including all prescription data** and they are growing to appreciate the potential usefulness of this data in identifying:-
  - like doctor shopping,

- diversion
- etc.

They're also very interested in the denominator issue and their felling is that:-

- there is not one denominator that's going to give you the golden answer about abuse
- but different denominators answer different questions and
- a number of them are relevant such as number of scripts or number patients exposed

And then of course from a **population data point of view** they are very interested in an obvious **important end come** which is:-

- **how many patients are admitted to detox for abuse of drug X ?**

B.14.j) Studies that illuminated the phenomenology of prescription opioid abuse

Also very interesting to them.

Because we know very little about who these people are and what they do.

So things that would be of interest to the FDA are:-

- studies to illuminate pathways to addiction,
- how did you end up like that
- did you start as a pain patient:-
  - if you did start as a pain patient:-
    - was that just in the background of probably substance abuse or other kind of mischief that you were associated with?

So **what are the pathways to addiction.**

They are very interested in **duration of recreational abuse** before some well defined endpoint like **a detox admission** as kind of view that as:-

- a potential marker of the "addictiveness" of a drug.
- How long it takes you to go from your first exposure or your first recreational use to the point where things are completely out of control enough that you're in a detox centre?

Also **qualitative research in prescription opioid abusers.**

- what do you like?
- Why?
- What don't you like?
- What puts you off?
- What are the attributes of a drug that might be more versus less preferred?

And then using various different populations to get this data and the ones that they mentioned were:-

- methadone patients,
- patients who had been to the detox center and
- potentially other populations as well.

C. DISCUSSIONS RELATING TO PROPOSED STUDIES

C.1. QUALITATIVE STUDIES

C.1.a) 1st Qual study - Attractiveness of the key attributes of modified release opioids (MROs) among prescription opioid abusers

Referring to focus groups, the street studies etc the things that Dr Segal and others were talking about.

And as examples of what might constitute attributes that are important to potential prescription opioid abusers when they're considering which drug would be good to abuse versus bad to abuse could be things like

- is there an antagonist in there,
- is it a transdermal formulation,
- is it a pill
- how easy would it be to administer it by alternative routes, snorting, injecting etc and

Also as a second component of this qualitative study:-

- to ask the prescription opioid abusers how they compromise the formulations

Potential issues for such a study

Potential issue # 1

- Is it a problem that the study would be conducted amongst people who had not been exposed to AP 48???

DISCUSSION +++ ABOUT HOW CREDIBLE WOULD A PRE LAUNCH QUAL STUDY BE FOR AP 48

Some KOLs felt that –

- they **would not be** people who were exposed to AP48 these
- would be just interviewing prescription opioid abusers to find out:

- what to them were the things that attracted them to abusing a prescription opioid

People obviously will bring whatever experiences they've had to the table but this is not meant to be a – "how did you feel when you were exposed to AP48 kind of a question"

Potential issue # 2

Duragesic patch is already so low in terms of abuse – so is there any point in creating studies to compare its abuse liability with AP 48?

- the Duragesic patch is not getting to the illicit market to any great extent
- it's not being diverted or there's a very low percentage
- diversion is already so low and
- the question is
  - if you're going to talk about lowering and looking at this, you don't have very much room to go.
  - It will be tough figuring out how much you could lower it further
- it's not like having OxyContin which everybody is abusing – and will give you a really nice control
- so one of the questions in this:
  - when you do have a preparation already which is so unabused:
    - is it even feasible to think that a product like this with naltrexone mixed in could be less abusable than the Duragesic reservoir?

Because you're going to be trying to offer the FDA that :-

- it's even less abusable than an already low abusable preparation

This question really transcends this individual study .

It's more like what's the whole point of trying to create studies that could compare the abuse liability of Duragesic reservoir with AP 48

However …….the counterpoint is:-

Yes, its true - Duragesic patches are very seldom abused. However:-

- that's not the question that's on the table now,
- the comparisons that are anticipated to be of relevance in a year or two are
  - how does the abuse liability of this AP48 product compare
    - not to Duragesic reservoir (which we've got 13 years of experience with) but
    - to matrix fentanyl (without Naltrexone) - a matrix system that it maybe possible to abuse much more easily, because it might allow the abuser to:
      - get doses sublingually,
      - split it up into unit doses,
      - to suck on it,
      - to eat it,

The idea is that abusability of matrix fentanyl which may emerge in a year or two maybe completely different from the abusability of the reservoir system that's currently on the market.

And it would be worthwhile creating methodologies that could tease out those distinctions.

The problem of credibility re including AP48 still remained …..

Some KOLs - not sure how having focus group with people who don't abuse something and they have no particular question, are really going to give you any information, if it's not there and they've had no experience, what information can you get from them

There is no experience on the street, so what is the point of doing it? How could the opioid abusers provide relevant and credible information??

Janssen have already

- demonstrated,
- talked about having data

- that it's not there:
  - the Duragesic patches are not being abused
  - it's not in the prescription opioid abusers armamentarium as a drug of abuse
  - so, because of the widespread lack of experience that people out there might have with abusing transdermal products would they be able to provide relevant information?

The one issue is that they are abusing OxyContin, they're abusing other preparations but they're not abusing the transdermals.

If the outcome of interest in this qualitative study is to evaluate a small number of people who have had experience in order to evaluate differential attractiveness, you'd ask the question

- whether or not people have abused OxyContin and Duragesic and
- they will give you some information about what makes the OxyContin more attractive whether it's related to the molecule or it's related to the formulation. That's the kind of information that you can get out of here.

It may be that there's a huge difference in the populations that have abused but all you have to do is discover the small number who have done both in order to talk about differential attractiveness.

This might be a study that could be done to look at:

- transdermal opioids versus oral opioids.
- not sure - especially pre-launch and before a few years are out there - that you could ever use this kind of paradigm to answer a question about the differential attractiveness between the matrix and the matrix plus naltrexone – because:-
  - then you're really talking about people that have experience with both.
  - They'd have to talk about whether or not the extraction process was harder with naltrexone

In defence some KOLs said …

It should be viewed more like market research.

You get a bunch of people – say 10 - , housewives who do laundry in a room, You say to them:-

- here's Tide
- it's got a red can,
- it's got a big screw top thing,
- it smells like this,
- this is how it feels
- this is what happens when you spill it on the carpet
- what could you think about a product like that that's not really on the market versus
  - here's something in a box:
  - it's a powder
  - it comes out in chunks
  - and that kind of thing

The whole premise of market research is that the stuff isn't on the market yet.

Another argument against …..

But the data already exist ….i.e. these studies have already been done…

There's already a good deal of research on what drugs are attractive to drug abuser and why,

so

- if we just examine the universe of attractiveness of drugs to the abusing population and
- then show by comparison that this doesn't have those attractive features
- we would be directly basically establishing the same point

For example studies by NIDA and other research places have established that:-

- fast-acting, fast-onset drugs are more attractive to drug abusers and the
- slow-acting, slow-onset ones are not

So we have a transdermal application - slow onset - so that makes it sort of a negative as opposed to something that might draw an abuser to the drug.

The answer is therefore to

- identify all of the features that make a drug attractive to the abusing population and then
- show by comparison that this particular target drug does not have those features

Another suggestion (constructive)

What about collecting this info in other clinical trials/studies?

Steve said - I have an open study funded by Janssen:

- now interviewing people coming in now
- a selective population - it's prescription drug abusers who are seeking treatment

But amongst that population these are the questions that Steve's group are essentially asking i.e.:-

- what they like about them, what attracted them to them and so on

But **drug abuse is** not a homogenous problem **...so** an additional value of qualitative studies **could be to understand the** concept and dynamics of 'hot spots'.

Drug abuse **is not a homogenous phenomenon and you're going to find certain areas and certain communities that are going to have a hot spot and the question is why and how likely is it to diffuse from there.**

So these kinds of questions are the type of questions that could be answered by a qualitative study.

Think about qualitative studies as

- focused ethnographic studies and
- more of a research process (rather than a specific kind of trial)
- that will allow you insight into what is going on.

To summarize-

The hypothesis that this study is addressing is that

- there are stable attributes of different kinds of prescription opioids that confer either:-
  - more or less attractiveness and
- one could quantify those if one designed the study appropriately (and it sounds like Steve is already doing something like that)

But again – remember ….

The OxyContin population is the large one …. So .. much easier to study…

Referring to Steve's study …

He's done 70 people so far - coming in for admission and

- all 70 are abusing OxyContin and
- two are abusing Duragesic – that's already telling us something about this

Once again the discussion came back to the issue that was worrying the KOLs

How credible is the focus group info if the patient has not experienced abusing the drug in question ???

If the patients, the individual doesn't have personal experience:-

- is the information gleaned from qualitative interview or from the focus group viewed as credible or
- are the data not credible - unless the person says oh yeah I've played with both and this is my feeling

The answer from the 'believers' …

What you're looking at is people who are:-

- drug savvy and the people that are:
- likely to show up doing it later on and – say - yeah I do the wash, (to use the earlier analogy) and:-
  - this is the kind of soap that really 'rings my chime' and that kind of thing

So Its

- informed opinion rather than scientific research
- from people who are drug savvy

Also - there is a sequential thought process that is associated with qualitative research …very often your qualitative study:

- points the direction for a survey or something that where you're going gather a lot of information and
- tells you how to ask appropriate questions.

Another thought /refinement….

It might be more appropriate to refer to pentazocine with naltrexone, i.e.:-

- use a drug that's already well known in the abusing community
- that has the antagonist built in and to
- have them say oh I wouldn't use that because it doesn't do anything - it has a blocker
- that would give you some transference to the product you're talking about -even though they're not familiar with it
- the concept of an antagonist, they understand perfectly well what that means
- they will recognise the pentazocine because that's been around a long time

C.1.b) 2nd Qual study - pathways to prescription opioid abuse

Who are the people that are abusing prescription opioids:-

- are they patients,
- are they collaterals,
- are they community abusers?
- Where do they get their drugs?
- What opioids do they abuse?
- Why do they abuse them? Etc. etc.
- just to try to understand the phenomenology of people who are abusing prescription opioids

Discussion +++ about the type of patients to be included

Type of patients to be included:-

- one population will be - those seeking treatment e.g.:-
  - people in detox centres and those who have a confirmed history
- people seeking treatment who say they use prescription opioids
- the other, will be - those not seeking treatment

You could advertise on the internet and ask and get people who are not necessarily seeking treatment which there's some experience in.

This would

- not be a prospective or predictive study it
- would be just talking to people who meet case definition and asking them how they got there

Again – think about the OxyContin population – lots of them ….

Don was amazed at how many OxyContin people they were seeing in their Out-patient detox center. He had been thinking about a project based on just asking them:-

- where they got their drugs,
- were they on heroin before they got to the drugs and
- what percentage of them had abused it as a consequence of therapy
- could be that some of these were people who had been doing fairly well and then all of a sudden they got exposed to OxyContin and then they got into trouble

That's a very interesting question which is particularly important but:-

- not sure it's relevant to this issue
- it's a very interesting basic science question

The question arises:-

Who should do these studies??? NIDA or Janssen?

Because in some respects some of these are very important questions that:

- may or may not be that linked to demonstrating that this product has a lower abuse potential

Perhaps …..

Trials/studies could be categorized into:-

- Those which are important for demonstrating differences in abuse liability between one opiate and another
- Those that are important for the world of research

Then Janssen can choose whether or not to fund that based on full clarity that that's indeed the case.

Another discussion point +++

Do you really need a separate qual study ?

Is this not - just a set of questions that you could add to a battery to any kind of study you're going to do

So - if you do a clinical trial

- you can ask the 200 people in the clinic trial

- as long as you're studying people with a history of prescription opioid abuse

BUT a Qual study per se offer additional advantages, i.e.:-

- in terms of a focused interview in which there's an effort to drill down and get a lot of information
- where you don't want to just ask the question where do you get your drugs,
- you want to know the phenomenology of that experience, and
- we don't really have an understanding of that,
- it's the only way of getting a detailed understanding of the phenomenology of the abuse experience
- therefore, it has to be a separate study

In conclusion ….

Perhaps an overall refinement leading to the best of both worlds

Actually, there is a natural way of complementing the various projects, i.e.:-

- apply your battery of questions within the trial and then
- select a sample - typically not more than 40 people - and
- do an in-depth qualitative interview and then
- subject that very lengthy data to ethnographic analyses using some of the content analyses packages

We would all agree that:-

- it could potentially be informative about any opioid including transdermal although
- it wouldn't inform about AP48 because
- this will be done pre-launch before anyone has any opportunity to abuse AP48

Could these studies be seen as characterizing mechanisms of diversion - giving you information about where a drug user is getting their prescription drugs?

This proposal is to:-

- interview people who are the end users and ask them about
  - where they get their drug

Now if everyone gets their drug from Joe down the street it's not going to really tell us whether Joe

- hoisted it off a truck or
- robbed it from a pharmacy, or
- went to a doctor and forged a prescription

So it may not be possible to get that very important information from this type of study.

Maybe there's another kind of study that we can come up with that could address that other very important issue as to what the sources are of diverted drugs.

Its amazing that even the DEA which obviously has it's job to try and cut off the sources of supply to the illicit market, seemed to be unable to come up with any information about how they decide where the drugs are coming from, aside from anecdotal reports, that did not seem to be systematically collected in anyway.

C.1.c) 3rd Qual study – doing focused ethnographic studies

These studies would be triggered by two mechanism i.e. developing:-

- a key informant network and also a
- a drug diversion network

Then based on potential problems that are triggered on information derived from these networks these would trigger focused ethnographic investigations to see:-

- is this report really representative of a problem or not and if so
- what's the nature of that problem.

These studies would get at a lot of the other information and tell us - from the users perspective:-

- what is actually happening here or
- whether it's some sort of myth or something else and
- the durability of the behavioural pattern

C.2. CLINICAL TRIALS

C.2.a) 1st Clinical trial - a randomised controlled clinical trial of AP48 this compound versus – a variety of different comparators

proposed in one form or another by just about everybody

Comparators proposed:-

- buprenorphine naloxone, in an analgesic trial
- fentanyl matrix without naltrexone
- short acting opioids

Patient populations - there were a few different proposals e.g.:-

- patients with chronic pain (obvious entry - you're not treated with an analgesic unless you have chronic pain)
- some suggested limiting the study or over sampling to just high risk patients

Outcome measures included a whole collection of words representing relevant constructs:-

- chemical coping
- abuse
- misuse
- addiction
- dependence,

So all this was basically summarising the notion of doing a randomised controlled trial with abuse related outcomes as the ultimate outcome measure.

These suggestions implied that these were valid constructs that would be measured.

But – the question was asked - how valid are these constructs - and the question was raised, whether Janssen should embark on a trial today with

what we have or try to do some validation or instrument development approach first.

Basic question of feasibility

Russ **wondered whether:-**

- anybody had had experience in other sample populations like this and
- what happens if you tell them that you're studying outcomes related to their abuse of the drug.

In other words if one went into an AIDS population with IV drug use as the risk factor and you gave them a consent form that says we're interested in studying you because you've had problems with drugs before and we'll be monitoring outcomes related to drugs and then we randomise them to two groups - to what extent can you do that study and make sense of it.

The danger here would be that just by the process of informing them of what the outcomes are you alter the potential to have the outcome handled

Howard – who had experience of researching these populations - suggested that one could ask about all sorts of health related outcomes, not just focusing on drug usage itself.

Not sure whether or not that makes a difference anyway but then the other part of it is that you have to tell them how they got selected – i.e. have to be up-front about this.

Simon also confirmed that in substance abuse studies it's done all the time - looking at a whole bunch of outcomes in the addiction severity index (ASI).

One may be asking people about:-

- how much money they've made illegally over the last year or last 6 months
- illegal drugs that they've used
- Even, how honest they are about responding

Apparently people respond to those things – surprising how often the questions yield answers that are not terribly socially desirable responses.

There are lots of studies done with AIDS populations looking at issues of safe sex and unsafe sex where people respond to the questions in what appears to be relatively honest kind of ways.

If it's done by computer you're probably likely to get a more honest response than if it's done by a face-to-face interviewer where there may be issues of shame or issues of concerns about legality.

There also may be

- proxy outcomes that one could look at that gain you something in terms of honesty
- things that are prodromal to actually stealing the drugs or abusing the drugs that one can look at in terms of substance abuse research

Remember also that the studies would be comparative – i.e. any bias is balanced across the comparison group as well as the drug of interest group. This was shown in Bigelow's study on anorectics in the 1980's where

- one group took all the drug they gave them and then some, whereas
- the other group brought back some of the samples saying 'you know this is terrific', and
- the drop outs were all in the group who didn't get the active drug

It was agreed that on the whole the study subjects would tell you about the 'rapes and pillages' and everything else they've done.

However, it was pointed out that the outcome measures were related to certain sorts of behaviours which are indicative of abuse but these behaviours have never really been validated.

In the absence of validated outcomes……

…the concern was that one would hit a floor effect because

- this is not a substance abuse population being studied for issues of abuse
- it's a pain population that have been given an analgesic and wanting pain relief

So there would be a concern there, that by intensively monitoring people, and by telling them what you're looking for in one way or another

- you reduce the incidence of the less egregious behaviours, the phenomenon that indicates the category of misuse and that
- maybe this is the kind of study - if it was large enough and long enough - that would look at more egregious abuse or diversion or episodes of addiction with the ASI, but wouldn't be able to look at anything less profound than that because of the floor effect that would come from the design.

There was discussion +++ about whether this type of study should be conceptualized as a post-launch (prospective) study and not a pre-launch study, for 3 reasons:-

- it should be done more naturalistically and it should go on for quite a bit longer, in order not to overly bias the sample – could look at how many people get started on an MRO, how many have to be taken off, etc
- you would need the actual packaged product that would be used in the marketplace
- you would need to do the AP48 versus the oral OxyContin otherwise you won't see a difference in the others because it's just fentanyl versus fentanyl

Doing it pre-launch would be doing it in more unnatural circumstances, that would bring out the biases that Russ was talking about even more.

For example, the kind of addicts you can trust to come in and be on a pain study for three months are not representative of the rest of the population who might get started on opioids and yanked off after a while for non-compliance.

C.2.b) 2nd Clinical trial – to develop a test to predict development of bad Outcomes

This is more of a prediction proposal to derive:-

- predictors of diverse "risk outcomes" – consisting of construct validation, instrument development meaning developing instruments to measure the outcomes of interest as well as a predictive instrument.

The trial would have to be done in several different phases: -

- beginning with a qualitative phase which could be focus groups
- then you might do a cross-sectional study to create an alpha version of a questionnaire
- then you might do predictability in a longitudinal study where you get patients and measure them at this point and then again at another point and then again
- chemical coping may be one of the constructs that we're interested in predicting the development of

So – to summarize - the purpose of this project would be to develop a test of some type that would predict development of bad outcomes that we're concerned about.

There would be two elements to it:-

- one element is an effort to provide better clarity about what the outcomes are of interest – could be a number of outcomes - related to a degree of misuse that didn't involve illegal or villainous behaviour or behaviour severe enough to warrant discontinuation of therapy and then
- more overt misuse and then
- abuse and
- addiction and
- diversion

This trial would basically be looking at the phenomenology of the bad outcomes in a way that allows an empirical basis for structuring those outcomes for the purpose of inserting them into clinical trials.

- Then the other aspect of this is to do a more traditional instrument development phase where you look at the predictive variables to try to find out what predictive variables might end up with these different outcomes

It's not really a trial, it's more a series of surveys that would end up with a validated predictive variables and the validated outcomes that would then allow that to be inserted into clinical trials

So this is really the pre-work that would need to be done.

Question re long time line required for this study – this particular study in total is likely to be long – so would the timeline be acceptable to Janssen? It would certainly be necessary to do in order to 'create the landscape'.

What about including some doctor measures?

The whole issue was discussed of behaviours and seeing substance abuse in pain patients but no one mentioned yet any doctor measures here..

It was mentioned that such a survey with Doctors was published asking them about what they thought about the different behaviours and that there was no consensus among them in terms of what they felt behaviours would be.

C.2.c) 3rd Clinical trial - To develop a way of assessing the abuse liability of opioids by doing a dual-purpose clinical trial

The dual purpose would be as follows:-

- In one way, the study could potentially provide the final validation for the predicted variables and the outcome categories. If you were able to do a study like that comparing a high abuse liability drug with a transdermal, (and these 2 drugs have tremendously different abuse liabilities) you might be able to determine what variables, are the really critical variables that distinguish these 2 groups
- The other way of looking at it is if you had enough information about the validity of your measures then that could be a study the primary aim of which was to show that a transdermal formulation in pain patients over a period of time is less abusable than another formulation

So, this could be in fact be viewed as being part of this research programme to develop an instrument to measure, to predict these negative outcomes

Type of patient - people with a relatively high likelihood of getting into trouble, like an AIDS population where 40% have pain severe enough to warrant opioid therapy. It makes sense to do that.

If to start with it was designed as a cross-sectional study looking at known abusers and known not abusers, it would be very quick to do

C.2.d) 4th Clinical Trial - Study to validate the results of urine toxicology testing for detection of abuse outcomes

There is an assumption that we know how to measure these abuse outcomes, that we have some gold standard for lack of a better term and then to try to determine what the results of urine toxicology mean in that setting.

Studies have shown that if you go to a pain clinic and take people on chronic opioid therapy, who the doctor thinks is doing fine you do urine toxicology on them something like 30% of them will have either an illicit drug in their urine or will have a non-prescribed controlled substance in their urine - something that you're not prescribing them that shouldn't be there is there.

But the problem is that while we all think that provides some interesting information nobody really knows what it means.

If someone has TFC in their urine does that mean they're not benefiting from their opioid or that they're addicted to their opioid or they're addicted to marijuana or what. And in the doctor patient encounter in the pain clinic we're desperate for more valid ways of diagnosing outcomes that are of concern to us and the question is what is the value of urine toxicology. So that's that proposal.

In New York there's a lot of poppy seed bagels ….

The same phenomenon is seen in methadone programmes because if you start with 100 methadone people after about 6 months with the dropout rates you maybe have 50% left. Between 6 months and a year, half of those will have illicit drugs in their urine so that issue which is here, the phenomenon that putting people on large dose of chronic opiates will in a sense reduce all other substance abuse behaviour is probably not a valid one

However, many of these diagnostic projects could be folded into the clinical trials. You could put into your clinical trials urine analysis periodically, then you can do some of this predictability testing - without having this be a whole separate study

C.2.e) 5th Clinical Trial To derive signals that are suggestive of greater or lesser abuse liability from Clinical Trials

Signals such as:-

- Degree of compliance
- signs of diversion
- signs of iatrogenic addiction
- unwarranted dose escalation
- use beyond what they need

It would be worthwhile to somehow compile all these signals in a systematic way from a body of clinical trials and relate that data from one medication to another.

This idea came from a meeting with the FDA. It's something that FDA staff are talking about, especially the Controlled Substance staff who are now at times saying - we want to see real world stuff from clinical trials.

The only problem is that people haven't been collecting these data, so you can't go back to literature and get these data. You've got to build it into the study

But that's why the word 'signals; has been used, which is a word many in the field are using, and the FDA staff understand that's all you're going to get but that it may be valuable.

Don Jasinski backed the 'signals' idea, mentioned originally by Jack, by saying

- firstly, for the last three or four years in all the abuse liability stuff and discussions FDA have actually asked for people to take data from the particular clinical trials, for example, for measuring dependence of the

drug, answering that question of the Controlled Substance Act, is when people stop the drug in a trial are they seeing withdrawal symptoms

- secondly, the FDA were proposing a project (in which Don was asked to collaborate) which was a proposal basically to develop methodology to help them try to develop instruments to do some of this.
- Thirdly, that they/FDA recognised that a study that shows positive results, positive diversion is stronger than one which is negative because in a lot of the clinical trials you have selected populations which have very tight control of the drugs, so there maybe not a chance for diversion although when it occurs occasionally it's a very important issue – so it should be included in all Janssen clinical trials

Feasibility might be an issue - but there's some relatively simple things that they've asked to see. If you do a clinical trial and you're using a controlled substance:-

- can you account for all of it,
- has any of it been diverted

The basic issue is - do your records account for all of it across all of your clinical trials?

One could explore that retrospectively,- that particular signal is going to be in the records for all clinical trials, if they relate to a schedule 2 drug.

Other examples of signals:-

- people come on the last day of dosing and they leave and so the issue is they're not followed up for a week or two afterwards to see if they have any withdrawal symptoms, any problems
- the other issue is - like the smoking studies - is to go 30 days later to do phone surveys of patients to see how you're doing and how did you do when you stopped the drug

Those are things that you can build in to get some information as a signal

Discussion +++ on including 'signals' in clinical studies …. Conclusion ….

Use an expert group like this to try to come to a sort of consensus as to

- what half a dozen or so measures are feasible to plug into a trial
- that would give you meaningful signals so that
- when you go to the FDA
- you can say we've thought about this, and
- this is what we've viably come up with in this light

C.3. EPIDEMIOLOGY STUDIES

C.3.a) 1st Epidemiology study - to develop an addiction susceptibility instrument

This was the goal of several of the other studies discussed earlier that attempted to approach that through different methodologies.

Here the approach is through epidemiological methods to develop an addiction susceptibility instrument by doing:-

- a case control study of patients
- cases would be patients entering detox for prescription opioid abuse
- controls would be non-addictive patients who are on opioids for chronic pain

So - same exposure, same disease - different outcome.

Then to do some structured interviews with those patients to determine

- whether there's a difference in the risk factors that those people had before or after they were exposed to opioids,
- whether certain risk factors have an association with the outcome of being a case versus the outcome being a control.

C.3.b) 2nd Epidemiology study - to validate prescription monitoring programme patterns for the detection of abuse and diversion outcomes

We have this prescription monitoring programme data.

We can determine:-

- what proportion of patients have 5 or more physicians i.e. are getting branded opioids from 5 or more doctors
- how many people run out of the medications early every month etc
- as well as combinations of such patterns

But the question is what does it all mean.

The same kind of analysis has been done on Managed Care Organisation claims data which were potentially really powerful as a mechanism for getting at that

Would it have to be a pre or post-launch study, i.e. when it starts to show up on the radar after it's available???.

if you assumed that the patterns that were indicative for abuse differed from drug to drug so a pattern of prescription monitoring programme that indicated abuse if you're being prescribed opioid A, might be somehow be different than if you're being prescribed opioid B e.g. AP48 then you'd need to cross-validate the data/patterns.

So you almost want to get the methodology and indicators down pat and then you can apply it to anything down the road.

C.3.c) 3rd Epidemiology study - prospective longitudinal epidemiological study - comparing abuse outcomes, (AP48 versus other modified release opioids*)*

A number of different proponents

Similar to the already discussed clinical trial except that this is an epidemiological study doing it in a naturalistic way

Population of interest would have to be defined:-

- could be chronic pain patients in general (where we have the problem of a low incidence rate)
- It could be high risk patients
- it could be just everybody in the community which is being done with basically everybody's risk management programme now

All these things could be done in clinical trials but, this would be a more naturalistic way of doing it.

???Value of doing it with a clinical trial approach vs. epidemiological approach??

The importance of randomisation - because for example, people may go on Duragesic because they are perceived to have a higher abuse potential – which could be potentially biasing …

All these studies transcend individual agents i.e. could apply to all opioids.

C.3.d) 4th Epidemiology study A nosologic analysis of problems related to prescription opioid abuse, (epidemiological approach

The idea is here is that we've got a lot of these national databases that collect a lot of data on a lot of different people. A lot of that data leads to:-

- what symptoms do you have
- what are the consequences of your abuse, etc
- all sorts of elements of problems that people may get into

The goal here would be to: -

- use those existing databases to see if certain of those symptoms cluster together and
- may represent syndromes that could then be named as being related to negative outcomes in relation to opioid abuse

Those names could be:-

- misuse
- recreational use
- dependence

So it's an empirical validation of what outcomes we're interested in.

This is an interesting approach because it could help define a common understanding and definition of:-

- what's abuse
- what's misuse
- what's dependence but …..

The fact is that we don't know that the categories that we would invent by putting our heads together are actually relevant to what's going on with people out there in the world.

And this approach takes the opposite approach - which is :-

- lets figure out what's actually happening to people and
- hen worry about what the name is

There are 2 ways of approaching this study.

- One way would be to use a categorical approach - which would be based on specified subgroups of symptoms (not necessarily limited to drug use) – they could include:
  - other kinds of co-morbid depressive symptoms that may be co-occurring

You can look at categories of responses that empirically emerge

- Another way would be look at it dimensionally - in terms of the outcome you might be interested in by doing, for example –
- a factor analysis - that looks at the different constructs that we're looking for

You could also look at different trajectories of abuse over time.

In terms of existing databases that will have this kind of information (in terms of the trajectories or any of the other aspects), there is the national co-morbidity study, the NESA which will be coming out with 50,000 people ….. household survey.

it does break out prescription opiates but the problem is that most of these natural data sets don't separate

- whether or not you had these problems as a result of being prescribed the drug and then used on your own versus
- just started on your own

So you can have heroin users that switch over to OxyContin versus grandma who's prescribed the drug and then starts to use it more.

But, you'd at least be able to see if the same things show in the in the prescription opiate versus other drugs – or whether there were differences.

This would be great to do as pre-work to the clinical trial.

It would test the same hypothesis or outcome categories as in a prospective trial but

- whereas a prospective trial would take a long time,
- this would be somebody sitting in front of a computer so
- this would be a great complementary study

C.3.e) 5th Epidemiology study - Pharmacy based surveillance system – nested case control

Designed to compare

- patients admitting problems with
- matched patients without problems

So again, the goal here is to again determine what factors distinguish

- patients that have problems with their prescription opioids, versus
- patients that don't

There are many ways to implement this.

For example - set up kiosks in a hundred pharmacies and when a patient picks up a prescription for an opioid they are invited to participate in a survey - they

- walk over to this private kiosk
- they put on their headphones
- they type away and
- they're asked questions about:

  - have you ever used up your drugs faster than you were supposed to
  - do you have multiple doctors
  - do you doctor shop
- do you steal
- what were your risk factors:
- did you have a bad life
- did your mother spank you
- do you have antisocial personality disorder - whatever the

There would be two separate goals (similar to the other studies discussed earlier):-

- one would be to
  - validate what the syndromes are
- what are people actually doing out there
- do certain characteristics form clusters
- the second one would be to look at potentially predictive factors for winding up like that

This focuses on people getting the drugs through legal means, in terms of picking up prescriptions.

Pharmacies might not want to develop space but then you could pay them, or give them a coupon for say 10 bucks worth of merchandise at the pharmacy for completing this survey, or an extra couple of drugs in your prescription.

If nobody is having any problems then

- the interview can be pretty quick

Or if they have more problems**:-**

- you can screen them and then
- either follow them up for more intensive interviewing in another study

- or do the questionnaires there in the kiosk.

This nosologic study would transcend specific opioids

C.3.f) 6th and 7th Epidemiology studies

You can begin to lay the ground work pre-launch and then you'd begin collecting data relevant to this particular drug post-launch.

The idea would be to set up:-

- number one - a key informant network which everyone will know from the work of Ted Cicero and others that have done this kind of work - and try to get
- local or regional signals about problems
- that may be arising
- that can trigger further investigations

These key informants would be set up amongst drug abusers or pain patients.

Key informant is somebody who

- has their ear to the streets or whatever the population is and
- you ask specific questions and
- then they respond

That information is then brought back to a central location and at that point is compiled and then a committee makes a determination - do you want to follow it up in any sort of way.

It gives you a kind of moving picture of what might be happening.

Key informants concept also includes checking in on web sites and chat rooms

- number two - local/regional drug diversion networks

D. MISCELLANEOUS POINTS/DISCUSSION ARISING DURING VOTING PROCESS AND DURING BREAKOUT PRESENTATIONS

D.1. MAIN VOTING CRITERION

There were 3 possible benefits for Janssen – envisaged in relation to the perceived value of the suggested studies

- first and foremost the studies would be - compelling to the treating community in demonstrating a lower abuse potential for using one drug over another drug
- second - if it works out, Janssen may very well use the studies from a regulatory perspective, to seek some labelling that speaks to a lower abuse potential and
- thirdly, - longer term - is there is something that showed that there was true lower abuse potential - is that something that Janssen could use in down scheduling, further down the road

But, the main criterion for voting on the studies today is in relation to their potential capability to convince people in the treatment community, of the lower abuse potential of one long acting opioid versus another long acting opioid.

However, regardless of whatever happens to scheduling:-

- the FDA will apply risk management and
- the issue of relative abuse potential assessment is going to be a critical determinant in what that risk management program will look like.

Possibility of down scheduling of new opioid by DEA

How would the DEA receive such a discussion?

Is there any body of evidence that the DEA would accept that this would create a climate for

- a realistic down scheduling ?

Bianchi said - certainly if Janssen made a convincing argument to the DEA

- they're required to consider the Company's petition
- the FDA and the DEA have to look at your proposal

BUT – right now:-

- OxyContin is shadowing everything
- it may not be a good time to do it right now but
- in the future - these new delivery systems could be more widespread and
- this will be ground breaking:
- to have something down scheduled as a result of the delivery system

So - the short answer is - yes the DEA would consider that.

An interesting angle would be if there was differentiation in the products that would allow the regulatory folks to differentiate as well,

if you're going to have unprotected products, and if there is a difference

- then, that would be a way that they could show some differences in the marketplace.

Janssen filing strategy at this point

- It's not a totally new NDA,
- it's bio-equivalence application strategy because
- THE product is bio-equivalent to Duragesic and
- the naltrexone is not in play in normal use

Some studies might be of very high value for a comparison of say AP48 versus OxyContin, but would have no value for comparison of AP48 versus generic fentanyl matrix patch.

D.2. BEST WAY TO COMPARE AP 48 TO FENTANYL MATRIX – WHAT IS THE UTILITY OF THE RANDOMIZED CLINICAL TRIAL PROPOSED EARLIER?

A study like this would be very important for exploring the relative abuse liability of AP48 versus any non-transdermal opioid

BUT

How about AP48 versus fentanyl matrix**?**

Virtually all KOLs say NOT IMPORTANT for comparing AP 48 vs. fentanyl matrix –

Because it won't show anything

Your hypothesis is that the naltrexone is inactive. So if you compare the two you're not going to see any difference. You're not lowering anything by doing this if you study it by the transdermal routes.

We are assuming only transdermal abuse?

The issue was raised about studying the injectable and other routes – this is really a clinical pharmacology study a human laboratory study because you're not going to do that into pain populations or clinical trials

Everybody is saying is that any differences in abuse liability or safety are going to emerge in the areas of

- diversion or in the areas of
- accidental ingestion

But are not going to emerge in terms of behaviours that will be different among chronic pain patients on these drugs when compared to the other.

Remember also - **that**

- the data that the regular Duragesic patch has not been abused
- should not be assumed to be the case when there's a fentanyl matrix around that has no naltrexone

Because:-

- now you're talking about a patch that you could use a hole puncher on and

- make a billion little oralettes out of it and so
- that's why the study has to be done of
- the AP48 versus one of these patches that may be generically made

The question is - if we were going to do an AP48 versus a so-called generic fentanyl matrix

- that would be a study for
- addicts
- possibly high risk pain patients - that's an enriched population

If the hypothesis was

AP48 is safer than matrix fentanyl in a high risk population such as

- chronic pain patients with a history of probably substance abuse or
- with AIDS from injection drug abuse
- or a population like that

This type of study would provide high quality evidence about differences in abuse liability in a clinical trial setting:-

- if the outcome was essentially a diversion

but there isn't a whole lot of standardisation of how to do that yet.

What you want to know is:-

- how many times do they take this whole punch and
- sell the thing

You can't chase them around to get that so the best you can do is give them extra patches and see if they bring them back to you.

You're getting into methodology that's not been standardised

These questions get answered more in the qualitative pathways of use so that this is not a good use of randomised clinical trials methodology

The outcomes that could be picked **up would be:-**

- patch tampering and
- diversion

So that's two sets of outcomes neither one of which has been validated as a good methodology.

Even in the high risk population – the experience in a high risk population is that those outcomes of diversion and tampering are not so prevalent

The logic of the experimental studies i.e. the hypotheses to be tested are as follows study, it may be grinding the patch up if that's what the study is.

(1) First hypothesis - is that the naltrexone, when it's placed in a patch:-

- will not be absorbed transdermally, i.e. naltrexone produces safety advantages over fentanyl alone, and
- will not affect the fentanyl being absorbed
- or affect the analgesia

(2) **Second hypothesis** - is that if it's misused and used by anything other than the transdermal route i.e.:-

- buccal or
- extracted and:
- injected or
- snorted
- the naltrexone will be active and will increase the safety acutely by:
- reducing the respiratory depression or
- the euphoric effects
- and the naltrexone will reduce the public health and social problems when people misuse it, either in terms of
- extraction, or in terms of
  - putting this in the mouth and sucking on it

(3) **Third hypothesis** – is that in the dependent person/addict naltrexone will increase safety by being aversive and precipitating withdrawal.

The way these are typically done is that you are supposed to give the drug the way it should be taken.

But here what you really want is - **have somebody try to divert the drug** and do this kind of

Will need to look (in the respiratory studies) also at the:-

- dose response curve for naltrexone to block the CO2 response curve.
- Bioavailability of naltrexone in the patches

D.3. PK STUDIES OF NALTREXONE – ADDITIONAL COMMENTS

There's only one ratio that exists in the patch.

The point at issue is whether or not the ratio protects at very small doses of naltrexone.

In other words:-

- if you carve the patch up enough to just give 100 mics of fentanyl
- you are giving just a tiny little bit of naltrexone, so the question is:
  - whether or not that tiny little bit of naltrexone protects for the shift to the CO2 response?. That's a very important study.

We know also that the ratio of naltrexone and fentanyl changes with use with the patch.

So all these trials have to be done with:-

- the ratio in the **unused patch** and
- the ratio in the **used patch**

And it has to be **the ratio in what's extracted -** not the one that exists in the patch

Also need to include (in PK studies of both fentanyl and naltrexone):-

- both drugs **in high dose**
- **longer patch use**
- **with and without heat application**

The data the company has – currently - doesn't really cover those three eventualities, all of which **will happen within the clinical setting**.

D.4. DURAGESIC ABUSE

We've heard in discussion over and over again the statement that **we know that Duragesic has a lower abuse potential than a lot of other opioids** – so 2 questions:-

- how do we know that? What data are out there right now that inform us that that's the case and
- of those data what can we apply then to AP48 to say OK we already know that for a fentanyl patch vs something else, so why can't we apply that.

There's several indicators –

- **first** is the **DAWN** data - when we do a request for specific forms of fentanyl abuse in DAWN – if it was:
- very, very low in the mid-90s
- it began to creep up at the end of the 90s and
- in 2001 data it showed that approximately half of the fentanyl mentioned in DAWN were Duragesic

But the actual **totals were still very small** and when you compare that with any of the other opioids it just doesn't even belong in the same pattern. So that's one indicator.

- The **second** indicator would be NFLIS which shows extremely low figures, suggesting that there's **little or no secondary market on the street with this material** of any sort. We don't have it differentiated into Duragesic vs other products
- And the **third** indicator would be the **toxic exposure surveillance system** which tracks:
  - over 2 million exposures to toxic substances every year
  - in 39 States and 3 territories and
  - picks up about 99.8% of the population in the United States

Each year - if you check it for fentanyl there's only very small numbers:-

- in 2002 data – there were - 4 anecdotal cases
- in 2001 data there were about 3-4 anecdotal cases of fentanyl patches in the toxic cases - the remarkable cases leading to death

So, anecdotally yes we do hear of the:-

- occasional abuse case
- we hear of experimenters and
- people who have thought of novel ways of chewing, biting, making tea out of it
- chickwick story was out there for a couple of years
- even have people who attempt to smoke it by extracting the ingredients and putting it into a cigar or pipe or whatever
- we have the occasional vaporiser, who tries to vaporise.

They all tend to end up in medical catastrophic consequences.

Death is not a positive reinforcing event…

So in terms of the actual evidence, it's mostly anecdotal….it's really sad.

Most of the accounts in the journal articles on Duragesic are **usually misuse** of the product by desperate pain patients. These are:-

- seeking additional relief or
- possibly trying to commit suicide
  But **not recreational drug abuse**, we just don't see it that often with this product.

So - **why is there so much effort being put into developing the matrix patch with naltrexone** if the original reservoir patch is so un-abusive ?

Well we know that the **generic patch will come out without naltrexone** and we could have done it but Janssen believe that there is a differential use potential for AP 48 vs. the matrix patch without naltrexone.

Naltrexone was picked because

- Janssen anticipated the abuse would be orally as opposed to IV
- Safer for accidental injection

Other Anecdotal stories ….re fentanyl patches …

Working in a hospital - if the count's short on one hydrocodone it's a big crisis. If you go to hospices and home healthcare and people are given fentanyl patches the nurses leave big supplies and if somebody dies for example in cancer, what happens to those drugs? Are they returned?

There have been stories about **people taking patches off patients**, leaving old ones on and putting the new one on themselves….also in **mortuaries**…

D.5. HOW IMPORTANT IS IT TO DEVELOP - A METHODOLOGY TO SEE WHAT THE EFFECTS OF THESE DRUGS ARE IN THE TARGET POPULATION ?

In conversations with the FDA and certainly at Advisory Committee meetings that's been pointed out as a huge flaw in this research area.

- FDA are concerned about and they are talking about it.
- It's not only been in this area - for example:-
- there was concern with some of the methylphenidate products that there was a lot of abuse by adolescents and kids. So they were talking about - could we get data in adolescents doing abuse potential.
- Nobody has done this before and lots of potential problems:
  - you use minors - emancipated minors
  - you get parents consent,
  - is this something that you can get through IRBs ?
  - is this going to be ethical doing the whole thing. ?
- But if you want to do it, yes, but it's going to take a lot of money and time because you don't have it established.
- It's the same issue with chronic pain patients ----
- All of us say yes it would be nice but that one of the issues is that you have **two hypotheses**:-
- one is that those **people in chronic pain programmes with history of substance abuse** who are causing problems are going to respond no differently than our addict population.
- If you show that, then you can support generalising from the addicted population
- On the other hand, **if they respond somewhat differently** then you may have a different population who is susceptible and you may have to develop this.

- The first scenario is the ideal one.
- There certainly seems a high likelihood that the first scenario will apply.
- A number of these patients who show up - how did they get started?
- They got started with:-
- their orthopod putting them on oxycodone,
- then switching over to other drugs.
- So that the people who've been through some of these studies in fact that was their **pathway to addiction.**
- So KOLs thought - there's a lot of leg work that has to be done at the beginning. And if Janssen want to do that, that's fine.

D.6. STEPWISE MODEL FOR DEVELOPMENT OF AN OUTCOME MEASURE (AS FASHIONED IN ONE OF THE BREAKOUT GROUPS)

Words used:-

- Misuse
- Aberrance
- Though we don't really have the label but we kind of know what we are talking about. Something that's not quite as rigid as a SCID diagnosis of dependence
- but something that would **capture the full range and importantly be kind of an ASI for this population.**
- So that it **would measure severity and change over time**.

First phase – item generation phase

Basically talked about going into an **item generation phase**

Where perhaps Janssen could bring Simon, Peggy Compton, the Group from Texas, Steve together, i.e. those who have tried to come up with measures of this concept in various forms to:

- pool their items
- talk about and do some concept mapping
- talk about all the different things that a measure like this would have to capture and
- just overwrite as you do when you do this, an item pool, a much longer measure than you would eventually need.

Next step - would then be

- a focus group of patients with chronic pain
- not just those who might have been in trouble with the way they use their medicine but
- just kind of more or less average people on opioids
- to get at may be some of the subtler things that we would probably miss if we focused on the people that really did the highly aberrant stuff

Next step -would then **go back to a group of patients and experts** and do the standard stuff:-

- have them read if for clarity, comprehensiveness, comprehensibility and so on.

Second phase – (after item generation)

Then when we had that final item pool, we would begin the process of trying to:

sample this on several different pain populations
with enough patients per group to give us a flavour of what the **range of the tool** would be **in patients at high and low risk**.

For example:-

- there are certain populations like **cancer** where the **risk is lower** vs
- **AIDS with substance abuse** which is **higher**
- **sickle cell, chronic pain**, etc. being somewhere in-between.

But also type them within their group:-

- potentially with maybe SOAPP or some scale like that
- get data perhaps on 100 patients per type of pain and then
- at that particular point in time **this measure whilst not anywhere validated would at least be available to use in the other trials (outcomes trials)**.

Third phase – (determination of reliability)

Do:-

- tests
- retest
- do internal consistency
- determine the factor structure of the measure,
- set about in a pretty standard way getting validity data as best we could on this
- link concurrent and construct validity to other measures ie compared to:

- clinician ratings of their patient's compliance or their regimen
- may be an ASI
- may be the Form 90, substance related problem scales, things like that
- may be PADT
- at various times just to talk about how well is pain management going for that patient, and
- perhaps a PMI thrown in, the Pain Management Index to get a flavour for how this all varies with a gross measure of adequacy of pain therapy

Fourth phase – (predictive validity)

And then also to get a predictive validity we could:-

- repeat this in **3 or 6 months** with a similar set of measure – perhaps also:
- adding in other checks on compliance like:
  - urines
  - pill counts
  - arrests
  - DWIs and
  - all the kinds of collateral damage that's done when people are not taking their medicines right.
- And then also – especially in the light of Howard's presentations – and because this adds to validity of this tool as well:
  - check things that we know ought to be associated with this concept (from the point of view of construct validity), like from the Household Survey e.g.:-
    - depression
    - anti-social personality disorder – which scale alone would be correlated .9 with this - since that was such a strong predictor in non-medical use in the Household Survey
    - gender differences
    - age differences, etc

You probably could do this with 4-5 sites or wherever you could get access to enough of people in those different populations.

Try to get about 500 patients to do it:-

- once a subset then
- for the test
- retest, and then
- everybody a second time and that
- would be probably on the order or about 400,000 to do that.
- Could do everything in probably 9 months – apart from predictive validity which would take longer
- could probably have this **scale ready to be used in the other trials in 6 months**.

When you are doing this **scale development** you end up with your **final scale as a subset of your larger scale** so other than the fact that's there's a little more subject burden and the initial items might be 150 whereas you really only want to use 26, - it's not so hard to ask those extra questions, so that you can get into the field without having a fully validated scale.

D.7. CONCEPT OF GRADATION OF ABUSE

This is the kind of concept where injecting a crushed up oxycodone is far more aberrant than running out of your prescription early once in a while.

So the issue of **weighting items is very important**.

Need good statistical knowledge to begin to talk about what one would have to do to add that, so that the **total score was a total of weights** perhaps not a total of just number of behaviours. But that's an important consideration.

But, we'd want to include enough not that bad behaviour so that you'd

- see some frequency and you
- could actually show a difference like
- early prescriptions or whatever, which is not necessarily a terrible thing.
- whereas clearly crushing up your oxycodone or cutting up your patch
  - represents obvious abuse,
  - may be less frequent in the general population.
  - and though it would be highly meaningful,
  - you'd also want to include some of these other items, **this would be important**.

This (instrument development and validation) may be the most important out of all of the projects being discussed, because without this none of the clinical trials or epidemiological studies can ever be done in a meaningful way, but

This is the kind of thing that's impossible to get funded.

Overall, It's the lack of capability of doing construct validation in instrument development that's been the main thing that's held this field back for a long period of time.

DEPRESSION - has the Hamilton

other fields have a standard score that everybody can use.

The idea here would be to **come up with the definitive instrument**. But then if Janssen is interested in opioids and is forced to be interested in potential abuse of opioids, it can be used in all the subsequent studies.

Traditionally - the pharmaceutical industry has not funded these kind of things because - it's like - what they deliver at the end is not usually in terms that's translatable to the senior management.

The NIH is completely out to lunch on this one – several attempts to get funding from them have failed.

In some respects the clinical trial is similar to what Howard was presenting.

D.8. WHAT WOULD BE A SUITABLE HIGH RISK PAIN POPULATION??? ??? AIDS PATIENTS

Actually:-

- most AIDS patients have neuropathic pain
- opioids are not first line therapy for neuropathic pain
- opioids in addicts with neuropathic pain is certainly not first

When push comes to shove a clinical trial will probably get done in **low back pain patients** and we will probably go in and:

- we'll do a SOAPP and
- we'll rate that
- we'll seek out people that are at high risk within a pain type populationand
- basically run enough patients given power considerations to look at
  - differences on this over time, perhaps out to a year – or even about 6 months trial
  - following people monthly with the PADT and other pain outcomes
  - running side by side with the misuse outcome.
- **needing to be discontinued** would also be an important outcome. In other words, if you
- start 100 people on AP48 and
- 100 people on oxycodone and
- you have to discharge from that therapy a whole lot more people because of oxycodone misuse
- that's a very important outcome and it
- avoids the ethical dilemma of
  - taking a high risk person
  - getting their addiction in motion and then
  - continuing the drug, which is something you really can't do.

So the target of such a study would be to enrol enough people and then use discontinuation as an outcome.

Other characteristics of a high risk population

The:-

- couldn't have current opioid dependence but they
- could have past opioid dependence and you require that
- they have current or past other kinds of substance abuse or dependence.
- Or if Simon's instrument has come up with some good cut-off points you could require a 14 on Simon's scale (if he's got the data that would allow you to come up with a categorical statement that this is a really high risk group).
- the idea would be to get a **really high risk group** so that within 6 months, say 30% of the people on oxycodone will have met some kind of criteria for abuse vs may be 15% of the people on the AP 48

Question -? is there anything that would be a **trigger and actually get you to identify someone who might be in an at risk population** and then follow those patients. Because you are looking for enriched design any way, by looking for people who are higher risk. There may be a way of doing that:.-

PADT would be a natural thing to have at the monthly assessments, but it's not intended as a screener so you still need a SOAPP or a TEXAS or something similar ahead of time.

Clearly, the study (on instrument development) would go hand in hand with the epidemiological study.

What's important/useful about this study is that, it can:-

help to design a more efficient epidemiological study
because then

- we will have some good estimates or better estimates of incidence and
- particularly in terms of sub-populations that that we might want to increase….

Also - this study **could start taking place right away**. So that by the time you'd be doing the post-marketing thing then at least you'd have this instrument that you could use.

D.9. DO'S AND DON'T'S IN CONTACTS WITH FDA

Don't use the term QUALITATIVE

if you went in with the term qualitative you would have problems with the FDA.

FDA are interested in and like to focus on:

- **science based projects** and even defining it as qualitative really makes it look like something different, which it may not be
- **various kinds of groups** and groups that they find pockets of abuse in like college students who might end up abusing the drug; other groups may be
  - casual/club users
  - casual other users, not necessarily involved with club drugs
- targets for risk management

D.10. ANOTHER DESCRIPTION OF CONCEPT MAPPING – (PROCESS) – WITH REFERENCE TO ATTRACTIVENESS

Look at:-

- these particular groups
- Potentially a continuum of risk - everybody knows that the street abuser is highly at risk but what about the kid who hangs out on Friday night
- identify groups that have to do with more and less risk.
- Include sellers - small sellers and large sellers; though they don't have to do with users, they represent another stake holder
- stratified by urban and rural populations
- gender
- ethnicity
- age groups

Then using ethnographic method,

- talk to people about what goes into the issue of **attractiveness** for them
- what makes a drug attractive or less attractive to them.

Then take that same breakdown and do concept mapping with that, - you get clear empirical findings.

Based on what people tell you within those cells:

- you come up with a particular stem and the stem might be:-
  - what makes a particular drug attractive to you.

If you take these people individually from these cells, and

- ask them that question and you say to them
- tell me as many things as possible that makes a drug attractive to you.

You get a long list of that, then you have those put into piles.

So you have different concepts of what makes a drug attractive.

You take those piles, you put them together from everybody that you've interviewed and then remove items that are overlap, etc.

You give this back to people, people make ratings about how important each pile is. What essentially you come up with at the end of that time is a scale of attractiveness of drugs and within different group:

- what attractiveness comprises may be very different from one another.

Then you bring other people back in again and you tell them about the drugs that you are interested in, it could be any set of drugs. I have a drug that does such and such, it's administered this way, it makes you feel this way and that way – what do you think of that, give me a relative rating of that. This scale might have several factors within the scale. What you come out with at the end of that is clear ratings about relative attractiveness of different drugs to different stake holders.

This study could be done in probably 6-9 months,

What's attractive about a drug to a large seller may be very different from what's attractive about a drug to a club user or a small seller for that matter.

But the results are very strong and very persuasive.

And again you also have the clear paper trail that the FDA looks for in these kinds of things.

in addition to the scales, you will get some **in-depth appreciation of these different groups** or members of the groups and what **they believe is attractive**.

Not to mention who you might have to target for risk management.

D.11. PACKAGE OF STUDIES – DURATION LESS THAN ONE YEAR

This Includes:-

- studies dealing with the bar of extractability
  - chemistry studies
  - physical studies
- single dose crossover trials addressing issues of abuse liability and safety and overdose in non-dependent individuals
- aversiveness studies in dependent individuals
- multiple routes of administration
- extended pharmacokinetic studies looking at fentanyl and naltrexone
  - fentanyl/naltrexone ratio
  - pharmacokinetics of naltrexone
  - extended periods of use
  - the heating patch studies
- qualitative research/studies

Here's the question - Looking at what could be done in less than one year, and taking all these together, could these less that one year studies make a persuasive argument that the AP48 product is less abusable that the fentanyl matrix is by itself?

Extraction studies and the **pharmacokinetic studies** are really going to be at the heart of the issue with respect to the Agencies. Safety and almost everything flows from that.

How would you think those would be configured? Which specific studies would have to be done?

Janssen would want to be able say – we've looked at the **chemistry** and **formulation** extensively. Here's what it takes to extract it, here's what it takes to abuse it. - whatever you can say about that. That would be critical for reassuring them.

This would be the core. This would be the starting point. Everything else would flow from that.

Janssen are going to have to have a **claim** – which is that adding naltrexone to this patch will make it less abusable.

So, you'd like to see a **subjective effectiveness** study, a **liking study**, that compares in some way fentanyl and naltrexone to fentanyl alone, and you see less abuse effects with naltrexone.

These studies will have to be done **orally and IV**.

Also will need to demonstrate the issue of **aversiveness** and that's going to be in methadone or morphine dependent people.

These are studies that will support Janssen's claims. In the end, that's the data Janssen have to show the FDA.

Another question – **how did Janssen come up with this ratio?** And is it going to project into humans too?

So quite apart from the FDA, Janssen (internally) have to make sure that it really works in the context of these sorts of studies.

For the first year, the key studies are going to revolve around ;

- anticipating what addicts will do and
- what can Janssen do thwart them ?

To say that we've had Duragesic and people have not abused it…that is an irrelevant experience.

Regarding **long-term epidemiological studies** – this is something that no other drug has been asked to do. So, Janssen don't have to demonstrate that to make claims about safety. But, this could be a post-marketing study and you have to follow people for a lot longer than they've been followed.

Re Chemistry studies – these would be the quickest of all of the studies outlined (based on experience with other studies of this type).

The studies would have to be divided in to the:

- physical extraction procedures

- chemical extraction procedures using commonly available solvents that can be purchased at the drug store, that a street chemist might be able to get their hands on.

The studies should be as simple as possible. They don't need to go into very great detail getting into the extremes of extracting it, but if Janssen can demonstrate that the most common ways cannot be effective in extracting the fentanyl, the Company will have served the community.

But we don't want the DEA or FDA to try it and see what their chemists can do and then find a flaw that we didn't find.

The simplest is the **buccal absorption.**

With **vinegar or olive oil**, there will be a relative extraction of fentanyl and a lesser extraction of the naltrexone…if you do that and you then get a certain concentration relative to fentanyl, give that extract to people (what are the ethics of that???)

That really is essence of the question to be addressed.

Janssen need to think beyond the buccal approach – need to give IV fentanyl and naltrexone together.

Need to have an idea of what the **subtle differences in the extracted ratio** could be, as demonstrated by biochemistry studies. Then ideally, put these ratios into the *in vivo* model. It seems like for oral administration, you might get away with that.

To mimic the 'real world' Janssen need to:-

- work with **defined ratios** of fentanyl to naltrexone
- work with patches at **different stages of use** ie patches that were
  - a day old
  - two days old
  - three days old

in terms of **aversiveness** - naltrexone may or may not get to the brain faster than fentanyl, so another question would be – what are the relative speeds with which both drugs get to the receptor?

Janssen should build on what ALZA has already done.

The marketplace will recognise 2 types of deterrent - the **learned** deterrent versus the **physical** deterrent. There are people who learn the hard way that they can't abuse Duragesic. So, from a safety perspective we need to understand early on about how addicts feel about this.

Regarding meeting with the FDA ….

The first impression is critical.

Need to go in with three basic points:

- **chemistry and extraction** – Janssen can say that the mechanism/combination basically works, it really is meaningful; it reduces abuse liability
- **perception of drug abusers**. - and that gets into the ethnographic studies - focus groups with drug abusers
- **studies with experts**

All these would point to the conclusion that this product would not be attractive to abuse. The point is that Janssen would have to do more than just walk in and say we don't think this would be attractive.

Concept mapping – could be a useful approach.

Concept mapping is a: -

- way of getting consensus
- statistical technique to look at qualitative data from focus groups.
- very useful technique – that gives numerical data and allows a variety of various kinds of statistical comparisons
- the kind of data that the FDA is going to be more and more interested in.

Also in the qualitative studies, Janssen need to represent the total spectrum of the abuser sub-populations – i.e. we're dealing with three separate populations here:-

- The quick (the ones who attend the pain clinics)
- The caught (the ones in the criminal justice system), and
- The dead – (the ones in post-mortem rooms) - the folks that find out the answers the hard way !!!

There is a grey area of users - a lot of them are not daily users, and Janssen don't want to miss that portion of the population. – need to represent the complete picture.

In conclusion – would the package of studies of less that one year (as listed at the beginning of this section) constitute (depending on how the data came out) a **persuasive argument that AP48 is less abusable than fentanyl matrix?**

By themselves they would not be **conclusive** evidence that AP 48 is less abusable, but these would be **positive indicators** that Janssen was heading in the right direction. They give Janssen a good rationale for why it developed the new product and to lay a foundation on which to lay out the rest of your clinical development plan.

Remember also that there are 2 perspectives - one is **convincing clinicians** and the other one is **convincing to the FDA**. There's opioids approved with no safeguards in them today, and if the unprotected matrix patch is approved …if that was thought to be safe enough, why would the protected matrix not be regarded as safer?

So, these data by themselves would not be **compelling**…both products might be safe enough to market. No one was going to produce something that nobody could figure out how to abuse.

But in the real world -. everyone is worried about OxyContin, so anything that works is a step better. Everyone is trying to be responsible.

It was interesting that after further, more detailed discussion, the KOLs were (as described later in this Report) almost unanimous in their conclusion that the package of these less than one year studies would be persuasive of lower abuse potential (depending on how the data came out).

How would all this interact with the reservoir formulation?

In a world of an unprotected matrix versus a reservoir, what kind of information could Janssen get to make people understand that these may not be the same from a safety perspective?

Janssen would need to do the same studies.

But, it also depends on how Janssen presents its case.

One of the issues is that Janssen's assumption is that fentanyl in a matrix patch could be a public health and social problem. And **that's what Janssen should sensitize the FDA to**…the reason Janssen haven't made a plain patch is because the Company thinks it's going to be a **public health problem**…abusers could just extract it and they can shoot it up. Moreover, if one just had the fentanyl in the matrix alone, it would be **easier to divert**. That's where Janssen should start from.

The Company does not want another OxyContin, and its contention is that another patch without the naltrexone could be another OxyContin.

That's really Janssen's argument. It starts from the same place. **Then if you add naltrexone**, you're going to reduce the abuse liability.

From 2001 to 2002, the numbers show that fentanyl is on the rise and, unfortunately, abusers of the reservoir patch who experiment and in many cases overdose, sometimes die.

Duragesic has been very safe historically, but in the future it might not be as safe – say over the next two years. Particularly when one looks at the enormous amount of Duragesic that's on the market compared to ten years ago.

So, AP48 might be acting as a pre-emptive strike in relation to Duragesic.

However, the presence of the naltrexone is not going to protect from the abuse of people who put on a bunch of patches.

If an unprotected patch gets out there, there is going to be in the abuser community a tremendous interest in the reservoir. These are not very clear thinking people. The word will get out if any of these patches work. That's what the Company should want to look at with some very quick consumer research.

On a **quick show of hands**. 11 of the 13 KOLs felt that **the package of studies (less than one year duration) as listed earlier would – on balance - be persuasive**.